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The Journal of Laboratory and Clinical Medicine

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ORIGINAL ARTICLES

CASES OF UNUSUAL ANEURISMS*

BY PAUL G. WOOLLEY, M.D., CINCINNATI, OHIO.

ANEURISMS are most frequently encountered in connection with aortic lesions, especially syphilitic ones, and are less frequent occurrences in the other vessels of the body, with the possible exception of the smaller arteries of the brain. Also, with the exception of traumatically produced ones, and an occasional one resulting from pure atheroma, they are the consequences of infection of the arterial walls. Even in the cases of pure atheroma there is a question whether or not that process is not fundamentally infectious. Aneurisms appear at sites of high arterial pressure and in situations where the arterial walls are weakened to a degree which permits of "giving way." In the aorta and in the cerebral circulation increases of blood pressure are less easily accommodated, other things being equal, than in the peripheral vessels where a larger area is available for taking care of increased pressures. Also in the peripheral vessels the arteriosclerotic processes are more apt to be diffuse, less apt to be focal, and therefore the common tendency to form a saccular aneurism is absent. There are, however, certain instances in which arteries of moderate dimensions are focally damaged to such a degree that a saccular aneurism develops. In some such cases the cause lies in some lesion outside the vessel, but gradually encroaches upon it until it is weakened and bulges. Such a process is common in tuberculosis. In such cases the vessel wall becomes involved in a tuberculous process which leads to focal dilatation, and sometimes rupture and hemorrhage. There are other cases in which the aneurism appears to be due entirely to a process which commences in the arterial wall itself, a process which is essentially the same as that appearing in the aorta in cases of aneurism. Next to the aorta, the popliteals, femorals, carotids, subclavians and innominate are the com-

*From the Mary M. Emery Department of Pathology of the University of Cincinnati, and the Pathologic Institute of the Cincinnati General Hospital.

mon seats of spontaneous aneurisms. Other vessels are less frequently affected.[1] The following statistics indicate the location of aneurisms in 530 cases tabulated by Crisp.[2]

Thoracic aorta	175
Popliteal artery	137
Femoral artery	66
Abdominal aorta	59
Carotid artery	25
Subclavian artery	23
Axillary artery	18
External iliac artery	9
Cerebral artery	7
Common iliac artery	2
Posterior tibial artery	2
Gluteal artery	2
Pulmonary artery	2
Brachial artery	1
Subscapular artery	1
Ophthalmic artery	1

The following series of cases illustrates these more unusual types of aneurism.

CASE I.

Not infrequently the innominate artery is involved in dilatations affecting the contiguous parts of the aortic arch. Less commonly the innominate artery alone is the source of the condition. The following case illustrates the latter circumstance:

J. K., Hospital No. A-1400, a colored man 51 years old, was admitted to the Cincinnati General Hospital on Feb. 25, 1916. He died two days later. He complained of shortness of breath. The family history was negative.

PAST HISTORY.—He had had measles, smallpox and chills and fever. He denied gonorrhea, but admitted lues. Except for these illnesses he had been a healthy man.

PRESENT ILLNESS.—On March 18, 1915, the patient was at work when he felt a pain in his shoulder, upon which he could feel a little "knot." He says that on that day he had carried a pine board over his shoulder and this he thought accounted for the pain. At this time he could not open or close his right hand. He went to a physician who told him he had an aneurism. Later he went first to one hospital and then to another and then, finally, he came to the Cincinnati General Hospital. Since then he has been admitted twice. He says that he has a cold sweat on the left side and that the left side of his throat feels cold and that he has a sensation as though phlegm is in his throat. He is dyspneic and does not speak easily.

PHYSICAL CONDITION.—The patient is a well developed, somewhat emaciated colored man about fifty years old, sitting in bed bent forward with his arms on his knees. He has marked inspiratory and expiratory dyspnea, with a harsh brassy sound. He coughs frequently, and the cough has a very metallic ring. The voice is likewise harsh and metallic. The left pupil is larger than the right. Both pupils are regular in outline. The left reacts to light and accommodation, the right slightly, if at all, to light. The conjunctivæ are pale. The teeth are in fair condition. There is some pyorrhea. The tongue is furrowed in the center and is covered with a thick yellowish coat. The throat is moderately injected. The tonsils are not enlarged. (During this part of examination the patient asked for water which he had a great deal of difficulty in swallowing. None was regurgitated through the nose.)

The veins over the right arm and chest anteriorly and the veins in the right side of the neck are dilated. The base of the neck on the right side at the right supraclavicular space is prominent, more so at the sternal end. On palpation there is a hard mass occupying this space over which the skin is freely movable. This mass extends over the junction of the outer and middle third of the clavicle to the left border of the supra-

sternal space. It is apparently continuous with the right carotid and right supraclavicular arteries. It pulsates visibly and palpably, raising the clavicle with each pulsation. No thrill can be felt. The chest is somewhat thin; the supra- and infra-clavicular spaces and also the intercostal spaces are marked on both sides. There is retraction of the left apex and all of the intercostal spaces and epigastrium. During inspiration the respiratory excursion is apparently equal on the two sides. On percussion over the right supraclavicular space there is marked absolute dullness over the mass described above. This dullness extends to the 2nd rib. Below this the percussion note on the right seems slightly higher pitched and shorter in duration than that on the left which is hyperresonant. The lower lung border on the right is at the 6th rib in the midclavicular line. Posteriorly a faint pulsation can be felt at the upper part of the supraspinous fossa on the right. Above the level of the spine of the scapula on the right percussion is less resonant than on the left. Below this the percussion tones are about equal on the two sides, and somewhat hyperresonant. The lung borders below are at the level of the 12th dorsal spine. Below this on each side there is about an inch of impaired resonance and then tympany extending down to the sacrum. On auscultation the breath sounds on both sides of the chest anteriorly and posteriorly are very distant. Inspiratory and expiratory sounds in the trachea are transmitted over the whole chest, interfering with the satisfactory auscultation.

The apex beat is seen in the 6th interspace 10.5 cm. to the left. Relative cardiac dullness, 12.5 cm. to the left in the 6th; 11.5 cm. to the left in the 5th; 7.5 cm. in the 4th; 3.5 cm. in the 3rd. Retrosternal dullness 7.75 cm. broad. Retrosternal dullness on the right is slightly greater than the dull area described above as extending down over the clavicle to the 2nd rib. With the patient in a sitting position the abdomen is lower than chest. Liver dullness extends about 3 fingerbreadths below the costal margin. The spleen is not felt. There is retraction of the abdomen on inspiration and bulging on expiration, especially in the epigastrium. No rigidity. No hernia. No masses and no tenderness palpable. Extreme knee kicks present. There are scars on both shins. There has been apparent recent loss of flesh.

The hands are cold. The pulse is scarcely palpable in the right brachial artery, and is absent at the radial, though well marked at the left wrist. The right arm is larger than the left and is apparently the seat of a very soft edema which pits only very slightly.

On auscultation over the apex the heart sounds are rather weak though clear. No murmurs are heard. At the base the sounds are still weaker. The pulmonic second is soft. The aortic second is almost inaudible. There are no murmurs over the aortic area. Over the mass in the neck the heart sounds were heard superimposed upon a sort of continuous roaring noise not definitely related to any part of the cardiac cycle. The blood pressure was the same in each arm, namely, 190 systolic, 110 diastolic.

Urine, Feb. 26, 1916. Amber, acid, sp. gr. 1,024; albumin present, no casts, few leucocytes, much cellular debris.

X-ray report February 26th. X-ray plate of chest shows a large opaque mass springing from the upper part of the mediastinal shadow and extending up into the right apex. The shadow is about the size of a large grape fruit, has rounded borders and is of uniform density. The heart outline is negative except for some accentuation of the upper left aortic curve. Lung areas and diaphragm contours are negative.

The temperature on admission was 99.6°, ranging between 100.4° and 97.6°. Pulse between 122 and 68. Respirations 30 to 38.

The patient had continuous difficulty in breathing and gradually grew weaker. He died quietly, apparently of exhaustion, at 5:45 A.M., Feb. 27, 1916.

CLINICAL DIAGNOSIS.—Syphilis; aneurism of the transverse arch of the aorta including the innominate artery; hypertrophy and dilatation of the heart; syphilitic aortitis; chronic diffuse nephritis; arteriosclerosis; congestion of the viscera; aortic and mitral regurgitation; chronic bronchitis; kyphosis; emphysema.

AUTOPSY PROTOCOL (C).

The body was that of a well developed, well nourished colored man of about 45 years of age, with a general glandular enlargement. The right suprasternal region was fuller than the left. The veins of the right arm were distended and engorged. The right pupil was larger than the left. The teeth were for the most part in fair condition. The gums were retracted and pyorrheic.

On opening the thorax, the lungs collapsed. The right lung was free. The left was bound down by firm fibrous adhesions to the lateral surface of the lower lobe. There was a mass in the superior mediastinum measuring 8 cm. in diameter, the upper limit of which was 3 cm. above the clavicle on the right side. The right clavicle was eroded at the sternoclavicular joint. The right lung was voluminous, crepitated throughout, and felt and looked normal. The left lung crepitated throughout the upper end, to a less extent, the lower lobe. The lower lobe, on section, was dark red in color, thickened, and from it a frothy, sanguinous material could be expressed.

The heart was enlarged and dilated, especially on the right side. The right auricle was filled with a chicken-fat clot. The tricuspid orifice admitted three fingers with ease. The tricuspid and pulmonary valves appeared healthy. The mitral orifice admitted two fingers. The leaflets of the mitral valve, as well as those of the aortic, showed no abnormal change. The papillary muscles cut with slightly increased resistance and were streaked with fibrous tissue, especially at the apices. The mural myocardium presented a slight increase in fibrous tissue. The entire myocardium was pale. The aorta showed scattered patches of fatty degeneration, but no sclerosis, or thickening. The mouths of the coronaries were patent. There was a sacculated aneurism of the innominate artery measuring 5 cm. in its greatest diameter, filled with laminated blood clot partially organized. This aneurism arose from the innominate artery about 3 cm. above its origin, and had an orifice 1 cm. in diameter.

The liver was of about normal size, was mottled yellow and purple, purple predominating. The capsule was not thickened, although there were a few stellate scars upon it which did not extend into the organ. On section, the interlobular veins were injected. There was a slight increase of fibrous tissue and fat. The spleen was very much larger than normal, was grayish-red in color. On section, the pulp was of a very dark color, the Malpighian bodies were visible though not increased. The right kidney was slightly smaller than normal, was pale red in color, the capsule stripped with ease leaving a granular surface. On section, the glomeruli were visible, the relation between cortex and medulla was normal, the line of demarcation was not distinct. The left kidney resembled the right in all respects.

The stomach, intestinal tract, pancreas, and bladder, except for a slight congestion, showed no abnormalities. The prostate presented a slightly enlarged median lobe which bulged into the bladder.

ANATOMIC DIAGNOSIS.—Innominate aneurism; cardiac hypertrophy and dilatation; chronic diffuse nephritis (interstitial); general lymphadenoid hyperplasia; chronic passive congestion of the liver, spleen and intestinal tract; prostatic hypertrophy.

REMARKS.

This is an interesting case from the standpoint of the arterial system generally. There was a history of syphilis, and there was an aneurism; there was accordingly a good chance that in the aorta at least there would be evidence of the infection. That there was no such evidence is unusual. This makes one wonder whether the aneurism was not therefore really a traumatic one, in spite of the fact that it would be difficult to strike the innominate 3 cm. from its origin. Still, stranger things have happened! The only evidence of lues in the body was furnished by the stellate liver scars—and they were not brilliant. Finally it occurs to one,—Morris suggested it,—that under the circumstances this case would have justified surgical treatment. Also it is interesting that aneurism localized in the innominate artery is not mentioned in Crisp's statistics.

CASE II.

This case is one in which the aneurism was localized in the superior mesenteric artery.

C. R., Hospital No. A-6412, a negro 25 years old, was admitted to the Cincinnati General Hospital on Sept. 25, 1916, complaining of pain in the belly, loss of weight, and

a mass in the abdomen. He died on October 9th. The patient had been in the hospital before. The following is the abstract of the previous history:

He was admitted on August 8, 1916, complaining of pain in the left side of the abdomen. This pain appeared suddenly while he was lifting and was just to the left of the midline and extended to the root of the penis. It was a sharp, continuous pain which did not radiate and which was relieved to some extent after bowel movements or urination. He had vomited once on the day before admission. He urinates frequently but has difficulty in starting the stream. Physical examination showed some emaciation, notched teeth; large epitrochlear axillary glands. There was slight dullness and bronchovesicular breathing over the upper lobe of the right lung. The heart examination was negative. In the upper abdomen, in the midline, or just a little to the left, was a mass which extended from xiphoid to umbilicus, and which was movable, not affected by respiration and tender. Over it there was tympany. The urine contained blood. The stools were normal. Cystoscopic examination showed both ureters excreting clear urine. The right was entered with trauma; in the left the catheter could not be passed. The bladder was normal. X-ray plates of the stomach were negative. Operation was suggested to the patient and refused by him.

The symptoms on readmission were the same. Physical examination showed that, as the patient had noticed, the abdominal mass was larger than before. This time the urine was clear and contained no blood or albumin. On September 30, an exploratory operation was done concerning which the following note was made:

"At the root of the omentum, surrounded by adhesions, a mass was found about the size of a small muskmelon, globular in shape but extending up under the stomach. It was covered with peritoneum. The abdominal aorta could be palpated posteriorly. The kidneys on either side were apparently normal. A fine needle was introduced and about 10 c.c. of a fluid withdrawn that was apparently blood. A large trocar with tubing attached was introduced and 20 oz. of fluid withdrawn. This fluid seemed to be almost pure blood but there was a cloudiness to it as it ran out as if mixed with a little pus. The trocar hole oozed a little blood after the withdrawal of the trocar but with a little pressure the bleeding soon stopped. A fold of omentum was stitched down with silk over the surface of the tumor where it had been punctured."

September 30.—The patient, after returning to ward had a very weak rapid pulse but was quiet and did not complain much of pain. Later he hiccoughed and vomited a good deal and was quieted by morphine.

October 1.—The condition very little improved; pulse weak and temperature subnormal.

October 3.—The patient seems a little better; complains of pain in upper abdomen.

October 6.—The patient in a stupor; pulse good.

October 7.—Still in stupor, breathing deeply, pulse strong.

October 9.—Stopped breathing suddenly at 10:10.

CLINICAL DIAGNOSIS.—Aneurism of the abdominal aorta; syphilis; generalized arteriosclerosis.

AUTOPSY PROTOCOL (G.-M.).

The body was that of a poorly nourished negro, about the age of 45 apparently, and about 5 feet 10 inches tall. The pupils were equal and not dilated. Arcus senilis was present. The eyeballs were sunken and the scleræ discolored but not jaundiced. Rigor mortis was present; postmortem lividity was present in the dependent portions. The teeth were in poor condition and cavities were present especially on the anterior surfaces of the incisors. Pyorrhea was present.

There was a transverse incision in the abdomen extending from the left nipple line to 2 inches beyond the right nipple line with the convexity pointing upward, the highest point being 2½ inches above the umbilicus. The incision was closed with catgut and seemed to be about eight days old. The tissues beneath were infiltrated with a dark blood and the omentum was adherent. In the left upper quadrant a mass was found 1 inch below the umbilicus and extending up to the costal margin. The omentum was adherent to this mass, which was in turn adherent to the stomach. The whole mass with the surrounding organs was removed and dissected. It measured, after dissection, 6x5x5 inches, and was adherent to the pyloric portion of the stomach, the duodenum, the ascending and transverse colon, and the lower surface of the left lobe of the liver. Behind it

was the abdominal aorta which also was adherent. The abdominal aorta was opened and then it was found that from this vessel an artery corresponding in position to the superior mesenteric passed into the tumor, which on being opened showed that it was an aneurismal sac due to dilatation of the artery. The sac was almost completely filled with blood clot, but at the proximal part contained a couple of ounces of blood. The intestines were congested and the urinary bladder extended about 1 inch above the symphysis pubis. The lower border of the liver was 2 cm. below the ensiform, and about level with the costal margin in the right mammillary line. The appendix was *in situ* and normal in appearance.

When the thorax was opened, the lungs collapsed and there was no fluid in either pleural cavity. On the right side adhesions were found at the lower border of the upper lobe and the anterior upper and outer surfaces. There were a few adhesions at the apex and adhesions were found between the lobes. The left lung showed lateral and apical adhesions. There was no increase in pericardial fluid. The left kidney was flabby, purplish-red in color, and on cross section was pale and the cortex thinned. The substance was very firm to the feel and the pyramids appeared fibrous. The glomeruli were visible as fine points. The capsule stripped with difficulty, was very thin, and on removal, tore the kidney substance in spots. The stellate veins were slightly congested. The pelvis was normal. The right kidney was similar. The liver was of normal size, with the scars of old adhesions over its surface. In the capsule there were numerous fine white lines that radiated from a number of points. At various points over the whole organ, stellate depressions and scars, due possibly to healed syphilitic gummata, were found. These extended into the substance of the liver at variable depths, the deepest being about 3 mm. Similar ones were found also in the substance. On cross section, the liver was pale pink in color, the interlobular vessels were readily apparent and the liver showed a slight yellowish tint. The bile ducts contained an unusual amount of bile and the organ had a firm feel. The gall bladder was distended, the wall slightly thickened and contained about 3 ounces of dark blackish mucoid fluid. The spleen was of normal size and the capsule about normal. On section the pulp was found to be very firm to the feel. The blood vessels were enlarged and stood out. There was an increase of fibrous tissue. The apex of each lung showed scars of old adhesions. All the lobes were bound together. The lungs were voluminous and crepitated throughout. On cross section, a frothy, blood fluid was exuded, which was greatest in the upper lobes.

The heart was slightly enlarged and the right side was dilated. The valves were healthy. The internal surface of the aorta showed a number of fatty plaques and in the descending portion below the origin of the transverse arch there were areas of subintimal thickening resembling luetic changes. The coronaries were not tortuous. The myocardium was pale and there was no macroscopic evidence of fibrosis.

ANATOMIC DIAGNOSIS.—Aneurism of the superior mesenteric artery; gumma of the liver; hepatic capsular fibrosis; luetic mesaortitis; generalized arteriosclerosis; splenic fibrosis; chronic diffuse nephritis and passive congestion.

REMARKS.

How infrequent superior mesenteric aneurisms are may be seen from von Schrötter's[3] figures as given by Lang.[4] In 19,300 autopsies an aneurism was found in connection with the superior mesenteric artery in but one instance, whereas there were four splenic aneurisms, one celiac, one renal, and three of the abdominal aorta. In the total number of autopsies 220 aneurisms were encountered.

In recent medical literature I have found several cases of mesenteric aneurisms, but all have been either traumatic or definitely mycotic and acute. Such are the cases of Gifford[5] in which there was a septic endocarditis, Rolleston and Whipham,[6] Cotterill and Miller,[7] and Stern.[8]

CASE III.

This is a case in which there was an almost extreme grade of generalized arteriosclerosis and in which a small aneurism was found in connection with the

almost completely calcified splenic artery. The case history is interesting chiefly on account of the symptoms associated with the general arteriosclerosis. It may be, however, that certain of the dominant clinical features had to do essentially with the splanchnic sclerosis in which the splenic artery was preeminently effected.

K. L., Hospital No. 6312, a white woman 63 years of age, was admitted to the Cincinnati General Hospital on December 1, 1915, complaining of "shortness of breath, heart trouble, lump in the stomach, and swelling of the right foot."

FAMILY HISTORY.—Her mother died at the age of 64 of "kidney trouble." Her father died at 63 of "abscess of the lungs."

PAST HISTORY.—She had measles, scarlet fever, and whooping cough in childhood. Ten years ago she had inflammatory rheumatism. Thirty years ago she had an ulcer over the left tibia. Sixteen years ago she had prolapsus uteri. She drinks tea to excess, but uses no alcohol.

PRESENT ILLNESS.—Last May the patient began to be short of breath on exertion. Her feet began to swell, the right more than the left. Later the abdomen became heavy and distended. The swelling gradually subsided. At the time of the onset she noticed two lumps, one on each side of the neck. The one on the left side comes and goes. For the last three months the patient has suffered with "indigestion," i.e., pain and distress after eating. She does not vomit, but belches and has a sour bitter taste in the mouth. For the last few mornings she has vomited stringy mucus which relieved the symptoms.

PRESENT CONDITION.—The patient is a poorly nourished woman. Her pupils react to light and accommodation. The conjunctivæ are slightly jaundiced; the eyelids are puffy. Both lids droop, the right more than the left. The teeth are poor. The gums are pyorrheic. The external carotids present two expansile enlargements, the one on the left being higher. These pulsating "kernels" are visible and compressible and appear to be aneurisms. The brachial and axillary arteries are tremendously sclerotic and tortuous and have a varicose feel that suggests focal dilatations.

The skin over the chest is dry, scaly, and lemon yellow in color. There is no tracheal tug. The apex is diffuse in the sixth and seventh interspaces outside the nipple line, lifting the left side of the chest.

The vocal fremitus is increased on the right. Posteriorly the right side shows tubular breathing, roughened at times with scattered mucous râles. On the left side there is roughened inspiration, tubular blowing expiration at the base and, in the axilla, tubular breathing. Anteriorly on both sides there is a tubular quality more pronounced on the right than on the left. There are no râles or friction rubs. On percussion the resonance is impaired over both apices posteriorly. The left was almost flat; the right was dull. Over the scapula on the right dullness runs off into a dull hyperresonance in the axilla and base. On the left the apical dullness was continuous with impairment over the scapula and upper axilla while the base and lower axilla show hyperresonance. Anteriorly under the clavicle on the right and left there is dullness fading into dull tympanites on the right, and impaired resonance in the left axilla.

There is a wide increase of cardiac dullness as follows:

To right	To left
4	5
4½	5
4½	9
4½	11½
5½	12
6	12½

On auscultation a systolic bruit is well heard at the apex and also at the aortic area. The second aortic is much accentuated and doubled at times. At times the bruit seems to be between the first and second sounds and not connected with them. At each beat there is a tremendous upheaval of the left chest. Blood pressure systolic, 240; diastolic, 145.

The abdomen is relaxed. There are no masses and no abnormal pulsation. There

is epigastric tenderness. The liver margin is made out 2 fingerbreadths below the costal margin. There is no hepatic pulsation.

Upon the extremities the veins are varicose, tortuous and knotty. There is evidence of old varicose ulcers. The reflexes are normal.

December 3.—The patient complains of a smothering sensation and of palpitation. She is conscious of violent heart action. The urine shows a trace of albumin and casts.

December 4.—An x-ray plate shows curvature of the spine and some displacement of the heart to the left. Just to the right of the aortic arch there is a large calcified gland. A further note on the plate says that the heart is enormously enlarged to the right, left and downward. There is an old fibroid condition at both apices. Very little lung is left on the left side.

December 5.—Urine excretion poor. Beginning edema of the lungs.

December 6.—Increased edema of the lungs. Patient lapses into unconsciousness. Pulse 120. Blood pressure, systolic, 200; diastolic, 120. Appearance of a petechial eruption. At noon, blood pressure, systolic, 180; diastolic, 90. Later Cheyne-Stokes respiration developed, and after remaining semicomatose until the following day at 5:15 P.M., the patient died.

CLINICAL DIAGNOSIS.—Mitral insufficiency; chronic nephritis; cardio-vascular-renal sclerosis; arteriosclerosis; varicose veins; hypertrophy of the left ventricle; edema of the lungs; anasarca; fibroid pulmonary tuberculosis; calcified mediastinal glands; possible aneurism of the thoracic aorta; passive congestion of the liver and spleen; chronic gastritis.

AUTOPSY PROTOCOL.

The body of an old, gray-haired, slenderly built, thin, woman of about 60 years. The abdomen seemed a little distended. The peripheral venous system was congested, so that the superficial vessels of the thighs, upper arms, thorax and legs showed very distinctly through the pale skin. There were well marked varicose veins in each leg, especially the left, and here the skin was generally thickened and scarred as though it had been frequently ulcerated. Both legs were slightly edematous. Posterior lividity was exceedingly brilliant, but it was patchy rather than diffuse, and appeared to be composed of numerous cutaneous hemorrhages closely set together. Both buttocks were mildly excoriated. The finger nails were dusky. The subcutaneous fat was scanty. The mammary glands were atrophic, but normal.

When the body was opened, the lungs did not collapse, because of a moderate edema and mild hypostatic congestion. There were adhesions at both apices. The liver border was 11 cm. below the ensiform and 8 cm. below the costal margin in the right mammillary line. The intestines were in normal position except the transverse colon which was very low and filled with large firm scybala. Except for the presence of two fibromata, the pelvic organs appeared normal.

The lungs (left 330, right 675 grams) contained just enough fluid and blood to keep them from collapsing. In each apex was a mass of calcium-containing fibroid tissue. They were congested posteriorly.

The heart (570 grams) was large and firm. The right auricle was tremendously dilated and filled with a large chicken-fat clot. The foramen ovale was closed. The tricuspid orifice admitted three and a half fingers. The valves were healthy. The pulmonary leaflets were healthy and the orifice normal. The mitral orifice admitted two and a half fingers. The leaflets were healthy except for a moderate edema of the margins. The aortic orifice was not dilated (1+ fingers). The leaflets were comparatively healthy. The line of attachment was a little sclerotic, and at the points of contact there was some adhesion. The free margins were thin. The myocardium was tremendously thickened, and the ventricular cavities showed practically no dilatation. The coronaries were not sclerosed. The aorta was the seat of a general atherosclerosis which was least developed in the arch and most in the abdominal segment. As a matter of fact the sclerosis was most intense, with the exception of the midabdominal section, in the main branches of the aorta, the iliacs, the celiac axis and its branches, the renals and the carotids, all of which were diffusely calcified and somewhat dilated. The dilatation in these vessels was more marked than in the aorta itself, where it was slight. The most strikingly changed vessel was the splenic artery which was exceedingly sclerotic and tortuous so that it looked like a large calcified twisted earthworm. At one point the vessel was dilated so that a small aneurismal sac the size of a small cherry appeared. Next in

intensity of involvement were the iliacs. The epicardium was thickened and scarred and the thickened areas were edematous.

The liver (1455 grams) was brownish in general color. The capsule was smooth and thin except for a patch about the size of one's palm on the anterior surface of the right lobe, where it was superficially thickened. The cut surface showed the early markings of passive congestion upon the yellowish brown substance.

The spleen (145 grams) was congested and deep purplish-red in color. The capsule was irregularly and superficially thickened. The substance was firm and in it the follicles could not be seen.

The pancreas showed no evident changes.

The kidneys (left 130, right 110 grams) were small. The capsules were removed with little difficulty though the granular surfaces were torn at a few places. The organs were generally mottled with red and yellow. They were evidently congested. The cut surfaces were firm and mottled. The cortices were thin.

The stomach contained a large amount of thin, bile-stained, cloudy fluid. The mucosa was congested and showed a few small pinpoint hemorrhages in the mucus-covered, slightly adherent mucosa. The duodenum was apparently healthy except for an increase in the mucus content. The bile ducts were patent. There were no gall stones in the gall bladder.

The uterus was small and atrophic. In the fundus was a large myoma, and near it to the left was a small one. The ovaries were sclerotic. There were no pelvic adhesions.

The urinary bladder and ureters were healthy.

ANATOMIC DIAGNOSIS.—Cardiac hypertrophy; dilatation of right auricle; aortic atherosclerosis; peripheral and splanchnic arteriosclerosis; arteriosclerotic kidney; obsolescent calcareous tuberculosis of lungs and bronchial lymph glands; fibromyomas of the uterus; varicose veins of legs; passive congestion of liver and spleen; chronic catarrhal gastritis; aneurism of the splenic artery.

REMARKS.

According to the figures of Crisp splenic aneurisms are very rare; according to those of von Schrötter, they are rare, but more frequently found than similar lesions of the renal or superior mesenteric arteries. Certain it is that in recent literature there are more references to splenic aneurisms than to most other forms of unusual abdominal aneurisms. In many instances the lesions appear to be due to embolic processes, as in the cases of Monroe,[9] and Walz.[10] In other instances, as in the present one, they appear to be definitely arteriosclerotic (luetic?) in origin.

CASE IV.

In this case the aneurism was associated with a congenital cardiac septal defect in a young infant.

D. B., Hospital No. A-7751, a white child 7 months old, was admitted to the Cincinnati General Hospital on November 22, 1916, for "shortness of breath."

There was no family history of tuberculosis or lues.

PAST HISTORY.—Except for an attack similar to that for which she was brought to the hospital, she has always been in apparently good health. She has been fed on Horlick's malted milk.

PRESENT ILLNESS.—This commenced five days before admission with cough and dyspnea.

PHYSICAL EXAMINATION.—The patient is a well developed white female infant seven months old, lying in bed crying and breathing rapidly and with difficulty. On admission the temperature was 100°, the pulse 120, and the respirations 38. The head is negative. The face is cyanotic and the respiratory movements are short and labored. The pupils are contracted and respond to light. The conjunctivæ are pale. There is no ocular deviation. The tongue is clean. The lower central incisor teeth are just emerging through the gums. The posterior pharynx is inflamed; there is a membrane. The nose is normal and there is no discharge from the ears. There is no rigidity of the neck. The finger

tips of both hands are cyanotic and the nail beds are deep blue. The chest is well formed and symmetrical. The respiratory rhythm is irregular and embarrassed. There is retraction of the peripneumonic groove during inspiration. There is dullness at the right base posteriorly, and crepitant and subcrepitant moist râles are heard throughout both lungs. Vocal fremitus is slightly increased at the right base posteriorly. The apices are clear. There is no distention or retraction of the abdomen. The liver dullness is normal. The spleen is not palpable. The genitourinary tract is negative. The toes of both feet are cyanotic. The apex beat is irregular and is visible in the 5th interspace inside the nipple line. The cardiac rhythm is regular. There is a harsh systolic bruit heard diffusely over the entire precordial region, but with a point of maximum intensity at the base, and apparently transmitted toward the apex, but not into the axilla.

November 24.—There is a distinct dullness over the right lower lobe from the angle of the scapula to the base. There is no dullness on the left side. Over the area of dullness there are crepitant and subcrepitant râles. Over the whole chest there are medium sized mucous râles. Anteriorly over the left upper lobe there is a breezy bronchial breathing without crepitant râles. On the right side the breathing is very rough.

November 28.—Over the right lower lobe there is still dullness but the râles are large and more moist. The general appearance is better. Respirations are not so labored.

December 2.—The condition is unchanged. Cyanosis is marked.

December 3.—The condition is unchanged. At 10:30 P.M. marked abdominal distention appeared and dyspnea and cyanosis increased.

December 4.—Death occurred at 8 A.M.

CLINICAL DIAGNOSIS.—Congenital stenosis of the pulmonary artery; patent foramen ovale; patent ductus arteriosus; bronchopneumonia.

AUTOPSY PROTOCOL.

The body was that of a well nourished girl baby, 73 cm. long. Rigor mortis was not present; postmortem lividity was slight. The pupils were equal. The lower middle incisors were present. The upper left middle incisor had just penetrated the gum. The body was still warm. There was nothing unusual in the peritoneal cavity except a moderate general hyperplasia of the lymphoid follicles. Apparently there was an increase in the number of visible hemolymph glands. The lower border of the liver extended 6 cm. below the tip of the ensiform and 4½ cm. below the costal margin in the right mammillary line. The peripheral lymph glands were not obviously enlarged. The thymus extended 4½ cm. below the sternal notch, was 4 cm. in width, and did not appear to be hyperplastic. It had two ascending limbs one of which passed forward anterior to, the other posterior to, the innominate vein.

When the sternum was removed, the lungs did not collapse. The lungs and heart were taken out *en masse* and as the trachea was cut across it was found to be practically filled with a thick yellowish mucoid purulent material.

The heart was of fair size but there was a tremendous dilatation of the right auricle, which was filled with a mass of deep red clot that was not laminated. The foramen ovale was open but seemed to be provided with a fairly competent valve. The tricuspid orifice admitted the tip of the little finger. The pulmonary orifice was tremendously contracted and permitted the passage of a probe not more than 3 mm. in diameter. The pulmonary artery itself was small. Immediately posterior to the pulmonary orifice was a very large orifice which led immediately into the left ventricle just below the aortic valves. The aorta was considerably dilated. The mitral orifice admitted the tip of the first finger. The aortic orifice on the left measured just 6 mm. in diameter and on the right, 1 cm. in diameter. There was evidently a defect in the interventricular sputum which permitted the pulmonary artery and aorta practically to join just above the muscular septum. The aortic leaflets seemed to be perfectly healthy, but the interventricular opening was not provided with any leaflets. The myocardium of the right side of the heart was somewhat thicker and more hypertrophic than that of the left side of the heart so that the right myocardium resembled more the usual musculature of the left heart. Both cavities were somewhat dilated, the left more than the right. The ductus Botalli was not evidently present, but in the usual position for it was what appeared to be an unusually large bronchial artery which led directly into the tissue of the right lung. This bronchial arterial branch led into a cavity, aneurismal in general appearance, just external to the right lung in the mediastinum, and was filled with a laminated clot.

The right lung was, as to the upper lobe and the upper two-thirds of the middle lobe, crepitant and healthy in appearance. The lower lobe and lower part of the middle lobe were filled with very numerous nodules in which there was no crepitation. On section, it appeared that these nodules were small foci of consolidation from which small, almost tubular casts of pus could be expressed. The left lung was, except for the presence of a few scattered patches of atelectasis, healthy.

The spleen was of fair size and measured 7x4x2 cm., was quite firm, a deep bluish-purple in color, and the Malpighian bodies were just visible.

The liver was large, quite congested, but showed nothing else unusual. There were no obvious lesions in the other organs. The kidneys, except for a moderate congestion and a certain amount of edema and some slight paleness, seemed to be healthy. The fetal lobulations were extremely distinct.

ANATOMIC DIAGNOSIS.—Congenital cardiac septal defect; patent foramen ovale; aneurism of an abnormal bronchial artery (right); acute lobular pneumonia.

REMARKS.

This very unusual case is interesting for other reasons than those associated with the aneurism. Nevertheless it is this that concerns us at this time. From the changes elsewhere in the pulmonary vascular tree it seems that there must have been some other factor at work than mere pressure,—that there must have been some toxic cause associated with the vascular anomaly. Throughout the consolidated portions of the lungs the vessels, branches of the pulmonary arterial system, were the seats of an extreme obliterating endarteritis, with which was associated thrombosis. The latter condition was most distinct in sections of the larger pulmonary arterial radicles in which these vessels are found to be almost completely filled with lamellated clots undergoing peripheral organization. In the smaller vessels there is evidence that many of them had been thrombosed and that the thrombi have been organized and canalized. In the smallest vessels the obliterating hyperplasia is clearest. It is probable that the agent which caused the clotting was also the cause of the weakening of the vessel that presented the aneurism. It is exceptional that this aneurism appeared in an anomalous bronchial artery.* Reference may be made here to a case of Weller[11] in which there was an aneurism of the ductus arteriosus.

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*For a general discussion of Congenital Heart Disease, see Hirschfelder, Diseases of the Heart and Aorta, 1913, p. 513, et seq.

TOXICITY OF HETEROLOGOUS AND HOMOLOGOUS SERUMS

By Carl E. Roser, Ann Arbor, Mich.

IT has been known for a long time that normal blood and blood serum are, under certain conditions, poisonous substances, some much more so than others; but the nature of the toxic action was purely a matter of conjecture until a few years ago. Before attacking the question of the nature of this toxicity, it may not be out of place to give a brief outline of the development of ideas in connection with blood injection phenomena. These conceptions are, in some cases, not directly related to the subject in hand, but will serve to outline the steps by which our present attitude had been reached.

The first observation of this kind dates back to the year 1666, when an account[1] of a sudden death following blood transfusion was reported to the London Royal Philosophical Society, the cause assigned being that of intravascular coagulation.

The next important work of which there is any record is that of Hippolite Magnani,[2] who made use of sheep blood injections into dogs. He found that in many cases the animals died very suddenly, and concluded that death resulted from too large an injection. The same observer also gave the first description of hemoglobinuria associated with such conditions.

Bischoff[3] believed that the toxic effects were due to the fact that the blood used for injections had not previously been defibrinated. Later he reported that this made no particular difference, and assumed that death was caused by the venous character of the blood.

Magendie[10] (1839) reported extravasation and hemorrhage in the lungs and abdominal organs as a result of injection of defibrinated blood, thus presenting a definite anatomical picture for a condition hitherto an object of little more than speculation.

Panum[4] was the first to establish the fact that the foreign corpuscles function normally for a short time and are then destroyed and excreted in the feces and urine. Brown-Sequard claimed to have observed the foreign blood cells one month after injection.

Landois,[5] in a series of experiments with whole blood injections, concluded that death was caused by the combined action of two conditions:

1. Destruction of red blood cells and liberation of fibrin, thus leading to coagulation of blood and the formation of thrombi in the pulmonary capillaries.

2. Agglutination of red blood cells and the deposition of masses of agglutinated cells in the pulmonary circuit.

Neudorfer[6] ascribed death under such conditions to the presence of unsaturated fatty acids, his idea being that the damage was done to the organism through the saturation of such unsaturated compounds.

Ponfick[7] injected defibrinated blood into the external jugular vein of a dog and observed respiratory symptoms coupled with other disturbances. He, however, discredited the hemagglutination theory of mechanical interference.

In 1877 Kohler[19] showed that fresh defibrinated blood, whether homologous

or heterologous, is an active poison, and ascribed toxicity to the presence of a fibrin ferment.

Moni[8] concluded that the toxic effect of the introduction of washed red blood cells was due to the hemolytic action of the serum of the recipient.

Batelli[9] held that serum must contain specific agglutinins in order to be toxic.

Gottlieb, Lefmann and Lefmann[10] studied the ether extractives of red blood cells and claimed to have demonstrated the toxic action of such substances on animals.

Coca[10] supported the contention that red blood cells contain certain substances, probably lipoids, which have a toxic effect when suddenly introduced into the blood stream of animals in large quantities. In summing up his own previous work he makes the following statements:

1. Cause of sudden death following injection of washed red blood cells rests in the clogging of the capillaries of the pulmonary circulation due to cell agglutination.

2. Presence of specific agglutinins in the serum of the animal is not in itself sufficient to explain the phenomenon. The additional fact of the interaction of a substance derived from the endothelial lining of the capillaries must be assumed.

3. Toxic substances in inactive form can be demonstrated in fresh corpuscles.

These ideas as to the mechanical nature of the toxic action of foreign blood and serum held sway in some quarters as late as 1910, for at that time three workers connected with the Rockefeller Foundation,—Loeb, Strickler, and Tuttle,[11]—brought out a paper in which they distinguished two kinds of serums; one, of which they said dog serum was an example, being hemolytic and coagulating, and the other,—beef serum—agglutinating. On the basis of these findings they joined the ranks of their predecessors and proclaimed the cause of death resulting from injection of heterologous serum as being twofold:

1. Stoppage of lung vessels with fibrin thrombi.

2. Stoppage of lung vessels with masses of agglutinated red blood cells.

During the past decade the study of serum toxicity has received great impetus through the discovery and development of immunity reactions and anaphylaxis. This was in part inevitable since serums played the principal role in such processes, and investigators were continually meeting with unexpected results from the use of primarily toxic serums. Besides this, the phenomena of anaphylaxis and serum toxicity were so closely related that it was necessary to investigate both in order to understand either. Careful research soon demonstrated that serum toxicity, whatever its real nature, was certainly not a mechanical process, as previous workers had supposed, and precipitation, agglutination, and hemolysis were assigned their true place—independent of toxicity.

Some such serums were found to have a much higher primary toxicity than others, so that a single injection of even very small quantities proved fatal in a very short time. Of such serums that of the eel was the most highly toxic, being one thousand times more active than the most anaphylatoxic substance yet produced. Human serum, as well as rat, beef, and goat serum belonged to this highly fatal class. *Novy*[12] finds that normal rat serum injected into a guinea pig gives a typical colloidal periodicity curve of toxicity, and that this toxicity

is very greatly increased by the addition of water. *Doer* and *Raubitschek*,[13] working in 1908, found that the purely toxic part of eel and beef serum was separate and distinct from the sensitizing and anaphylactic substances, and could be destroyed comparatively easily by heat and dilute acids. Thus, if the toxic portion was destroyed, it was found that the remainder was capable of producing all the phenomena of sensitization and anaphylactic shock. However, these observers, as well as *Kossel*,[14] showed that, as the primary toxicity of a serum increased, the hypersensitizing and anaphylactic properties seemed to decrease and were in some cases masked altogether.

Perhaps the most comprehensive work done in recent years on primarily toxic serums is that of *Zinsser*,[15] who utilized rabbits for making goat serum injections. He found that the severity of symptoms increased with the size of the dose and that the symptoms themselves were very similar to those described by Uhlenhuth and Haendel, as well as by Doer and Moldavan in connection with their work on anaphylaxis. He reported the following:

Latent period varying with the quantity injected from 1 to 10 min.

Respiratory distress.

Paralysis, beginning with hind legs.

General convulsions before death.

Following the work of Doer and Raubitschek, Zinsser investigated the nature and properties of the toxic portion of the serum he had used. He first tried to establish the relation of toxicity to associated characteristics of goat serum, such as agglutination and hemolysis, and to this end he utilized the previously demonstrated fact of the heat lability of the toxin. The serum was heated at 56° C. for twenty minutes, and it was found that both toxicity and hemolytic power had been destroyed, but that the agglutinating capacity remained. Reasoning from this result it was concluded that agglutination, at least, could not be regarded as the toxic factor, but the experiment had shown that the reaction of hemolytic and toxic portions were the same. Were they actually identical? In order to test this, Zinsser removed the hemolytic amboceptor and complement from the serum by allowing the latter to act on washed red blood cells until the hemolytic power was exhausted. The substance remaining was centrifuged to remove the cells, and injected into guinea pigs, with results that clearly indicated that toxicity was unimpaired. Hemolysis was, therefore, also ruled out as the toxic principle, and only two possible interpretations remained. The poison must be either an anaphylatoxin, produced by the action of the serum on the cells, or a heat sensitive toxin independent of hemolytic property. Further investigation established the latter as the more probable, for,

1. The hemolytic property of inactivated goat serum could be restored with guinea pig complement, whereas toxicity could not.

2. Toxicity dropped more than the hemolytic property on standing.

3. The toxic substance after removal of the hemolytic amboceptor and complement corresponded closely to the toxic dose of the original serum.

4. The toxicity of the fluid remaining after the removal of the hemolytic amboceptor and complement was destroyed at 56° C.

From these results Zinsser concluded that the toxic action of goat serum for rabbits was due to a heat sensitive substance independent of agglutination and hemolysis.

The question now arose as to whether the reaction might not be anaphylactic, but investigation soon showed that this was not the case, for, according to Zinsser, the reactions differed in the following particulars:

1. *Autopsy.*—No lung inflation; gross changes practically absent.

2. *Temperature Fall.*—"Although this does occur, it means but little, since in this case an active serum was used, distinguished from the inert protein matter used in such work."

3. *Diminution of Complement.*—Occurred in all cases in spite of the fact that the complement of the subject had been shown to have no part in the reaction. This was proportionally less than in true anaphylaxis.

4. *Antianaphylaxis.*—Rabbits which received sublethal doses showed no increasing resistance to subsequent injection. "It appears certain that nothing of the kind takes place."

5. *Fall of Blood Pressure.*—Preliminary rise followed by slight fall and rise to normal. In young rabbits fall was rapid and continued until death.

6. *Etherization* did not prevent death.

7. *Atropin* had no effect.

Doer and Raubitschek,[16] and Uhlenhuth and Haendel[17] had shown the same thing by heating the serum at 56° C. and finding that the toxic portion was destroyed while the anaphylactic portion remained.

Like other toxins those of normal serum produce antitoxins which protect against future injections. This process goes on simultaneously with that of sensitization in serums, such as the eel, which possess double antigens, so that it is possible, as shown by Doer and Raubitschek, to have an animal immunized to eel toxin and sensitized to eel anaphylactogen, with the result that on the second injection a double process occurs; namely, that of toxin binding and anaphylactic shock. This double phenomenon can further be demonstrated by transferring blood from an injected guinea pig to a normal animal, and thus establishing, on the one hand, passive immunity to the toxin, and on the other, passive sensitization to the anaphylactogen. It can, therefore, readily be seen why it is impossible to immunize an animal against such serums; immunity to the toxin can be established readily enough, but there can be no immunity to anaphylaxis, and it is the latter which produces the symptoms or kills on the second injection.

As to the actual nature of this toxicity, nothing absolutely definite is known. Early experiments with defibrinated blood had naturally enough suggested the idea that toxicity was associated with coagulation, and investigation seems to have confirmed this, as the following experiments by Novy[18] indicate.

If rabbit blood is taken and transferred directly to a guinea pig at high speed—30 secs. from heart of rabbit to vein of guinea pig—no toxic action is evident. However, if the animal is bled and the blood defibrinated, toxicity becomes evident, and furthermore, it is found that the degree of toxicity varies with the mode of defibrination. Thus, if defibrination is accomplished by shaking with glass beads the product is highly toxic, whereas defibrination with an iron wire yields a blood of mild action. Serum obtained by rapid centrifugation of defibrinated blood is also poisonous.

The relation of such toxicity to coagulation has brought forth a variety of theories. *Kohler* ascribed toxicity to the presence of the fibrin ferment; *Studzinski* held that the poison might come from mechanical disruption of the red

blood corpuscles, and *Freud* thought that the poison came from injury to the blood platelets. No one theory explaining the phenomenon has been accepted, at least each has found its opponents, so the whole matter must still be regarded as an open question. However, we may accept the statement of *Vaughan*[19] that "serums, even of homologous origin, behave like foreign proteins possibly on account of changes that take place during coagulation."

This *primarily* toxic property of serums, while of great interest and importance, is far outweighed in significance by another phenomenon associated with the poisonous action of serum, namely, that of hypersensitization or anaphylaxis. This phenomenon is not in the strictest sense a toxic action, since it has definitely been proved that no toxin—used in the sense of a substance which calls forth an antitoxin—is involved. However, considering our subject from its broader aspect, namely, toxicity in the general sense of poisoning, the question of serum anaphylaxis cannot be omitted. A brief outline of the development of this subject will perhaps serve to give a general viewpoint not otherwise obtainable.

As early as the year 1839, Magendie noticed that if an animal received an injection of a given substance, and later received a second injection of the same substance it usually died immediately, or at least after a very short time. However, neither he nor his contemporaries followed up this observation so that it was soon forgotten.

The early observations made by *Behring*[20] and his pupils (1893) in connection with complications arising from the use of antitoxin, as well as similar conditions noted by others with regard to tuberculin and mallein, are now regarded as purely anaphylactic phenomena, but at that time more or less labored explanations were formulated on the basis of Ehrlich's side chain theory of immunity. It was not until 1898 that the fundamental observations now at the basis of our knowledge of anaphylaxis were made by *Hericourt* and *Richet*[21] while working with eel serum injections into dogs. They observed that repeated injections gave an increased susceptibility to the serum instead of the expected immunity. Later *Portier* and *Richet*[22] made similar observations while working with "Actino-congestin," a poisonous substance derived from the tentacles of Actinia. This substance in minute doses produced severe symptoms and death in dogs. If a sublethal dose was given and a few days allowed to elapse before a second injection was administered, it was found that one-third to one-fifth of a lethal dose produced death. From these experiments it was concluded that the first dose had given rise to a well marked increase in susceptibility so that on the second injection a very greatly decreased quantity produced severe symptoms and death. Richet coined the word anaphylaxis (*ανα*-against; *φυλαξις*-protection) to distinguish this phenomenon from immunity or prophylaxis. This term has since been shown to be a misnomer (Vaughan).[23]

Shortly after Richet's earlier experiments, Arthus[24] made a series of observations in connection with the repeated injection of horse serum into rabbits and worked out a condition which has since been known as the "Arthus Phenomenon." He repeatedly injected horse serum subcutaneously at short intervals, and found that he was able to produce an intense local reaction which, with continued dosage, progressed from a mild edema at the site of injection to a

hard induration followed by subsequent sloughing off and ulcer formation. This showed that with each succeeding injection the susceptibility of the animal was raised until a point was reached where the same quantity of serum which had at first caused only slight edema was capable of producing such intense action that sloughing of tissue resulted. An observation very similar to that of Arthus was made by Theobald Smith[25] in 1904. He noticed that guinea pigs injected with mixtures of toxin and antitoxin in the course of antitoxin standardization died if after a short interval they were reinjected with normal horse serum. At about this time Otto[26] and Rosenau and Anderson[27] made elaborate inquiries into the nature of this reaction and succeeded in bringing out many new points, such as specificity of the reaction, transmission of hypersensibility to the offspring, etc. "Die Serumkrankheit," a treatise by von Pirquet and Shick[28] also appeared at this time. The breadth of the biological principle involved was shown by Vaughan and Wheeler,[29] Nicolle,[30] and others who demonstrated that the reaction was not confined to animal serums but was elicited by proteins in general.

Needless to say a phenomenon of so striking a nature at once made its influence felt in other directions and the mechanical obstruction theory of serum toxicity began to lose ground. It now became an object to establish definitely the relationship of anaphylaxis to the associated phenomena of hemolysis and agglutination. The researches of a number of observers soon established this. Uhlenhuth and Haendel[31] found that inactive beef serum activated with guinea pig complement was able to hemolise guinea pig red blood cells in vitro, but had no anaphylactic action; they therefore said:

"The anaphylactic substances are probably not identical with hemolysins, hemolytic amboceptor or complement."

Doer and Moldovan[32] reported findings similar to the above but disagreed with some other observers who claimed to have destroyed hemolytic and agglutinating properties without injuring toxicity by heating at 50° to 60° C. Attempts to separate the hemolytic and toxic properties by either chemical or physical means—heat, alcohol, carbon dioxide, dialysis, etc.,—failed entirely, in fact a remarkably parallel reaction was evident. However they too believed that toxicity and hemolysis were separate, and summed the matter up by saying, "Toxicity is independent of hemolysis even though it is caused by the same amboceptor." The same authors "find it reasonable to suppose that toxicity is referable to an excessive precipitin reaction."

The latter statement is in direct line with the conclusion at which Friedberger[33] arrived, namely, that precipitation and toxicity are simply different phases of the same reaction. In other words no differentiation other than a purely quantitative one can be made between precipitation and toxic amboceptor. This idea will be more fully discussed with the theories of serum toxicity.

No one, of course, doubts any longer that the so-called secondary toxicity of serum is identical with anaphylactic shock. Doer and Moldovan, for instance, find that the symptoms following injection of normal serum are not only externally but from their very nature anaphylactic in type; guinea pigs show the typical Auer-Lewis phenomena and symptoms can be antagonized through the use of atropin.

The relationship of this type of serum toxicity to associated phenomena is well expressed by the following quotation from Vaughan's "Protein Split Products."

"It seems most probable that anaphylactogens, agglutinogens, precipitinogens and lysinogens are identical. In other words one group in the protein molecule causes the animal to develop a substance which, under certain conditions, may act as an agglutinin, precipitin or lysin. We are inclined to the belief that the same ferment may, under varied conditions, act as an agglutinin, precipitin, lysin, or it may cause a deeper cleavage of the protein molecule resulting in the liberation of the protein poison."

The principal symptoms accompanying so widely known a phenomenon are, of course, definitely known and the accounts of various workers are very much the same although differences do arise from the use of different experimental animals. The most evident symptoms as described by Vaughan[34]—less concisely by Auer and Lewis,[35] and Gay and Southard,[36] and Biedl and Kraus[37]—make their appearance in three stages. The following quotation from Vaughan's "Protein Split Products" is an accurate description of the principal facts available:

"The first stage is that of peripheral irritation. The animal is excited and evidently itches intensely as is shown by its attempts to scratch every part of its body that it can reach with its feet. The second stage is partial paralysis. The animal lies on its side with rapid shallow and difficult breathing. It is disinclined to move and when urged to do so shows more or less incoordination of movement and muscular weakness, with partial paralysis especially observable in the posterior extremities, which it drags. Rarely the animal dies in this stage. The third or convulsive stage, begins with throwing back the head at short intervals. The convulsions become more general, more frequent and violent, and the animal having reached this stage, usually dies in a convulsion or immediately following one. Expulsion of urine and feces is common in the convulsive stage."

While the above symptom complex is described in connection with animals treated with Vaughan's protein poison, it is also an exact picture of conditions arising from anaphylactic shock produced in the usual way.

Observers are not altogether agreed as to the autopsy findings in cases of anaphylactic death. Gay and Southard were the first to make a thorough study of this phase of the question, and they came to the following conclusions:

Tissues of animals (guinea pigs) examined during the anaphylactic phase, that is, during the period of incubation between the first and second injection, show no lesions. However, the toxic phase is marked by striking changes. Eighty-five per cent of the animals dying after the second injection, or being killed within twenty-four hours thereafter, show macroscopic hemorrhage in one or more organs. The stomach leads in frequency of involvement (55 per cent) and the lungs come next in order (40 per cent). Other localizations of hemorrhage are to be found in the brain spinal cord and peritoneum. Hemorrhage is associated with widespread fatty degeneration of capillary endothelial cells, heart muscle, peripheral nerves, voluntary muscle and gastric epithelium.

Rosenau and Anderson[38] found congestion and sometimes hemorrhage, but

they say that these lesions are not always apparent and are not specific. Furthermore, they were unable to demonstrate fatty degeneration.

Auer and Lewis studied the lung picture at autopsy and found the lungs greatly distended and filling the entire thoracic cavity. On opening the chest the lungs failed to collapse and even on section showed no decrease in distention. The alveoli and air cells were filled with air imprisoned by the tetanic contraction of the muscles of the bronchioles. Slight edema was also noted.

Vaughan, in using his protein poison, which he has demonstrated as being identical with the anaphylactic poison, finds that in the pure state parenteral injection of the poison causes no lesions of the kind described by Gay and Southard, but if an incompletely purified product is used, intense hemorrhagic peritonitis results.

The findings of Gay and Southard, as well as Auer and Lewis, were confirmed by Biedl and Kraus, and it is to the latter that we owe the most satisfactory demonstration of the mechanism of anaphylactic shock.

As might be expected, Gay and Southard, being the first to describe the lesions associated with anaphylactic shock, immedately concluded that these were the direct cause of death. On this basis they held that the respiratory symptoms were due to a lesion at the respiratory center, the same reasoning applying to the other symptoms as well.

Rosenau and Anderson, while differing with Gay and Southard in the matter of the gross lesions, agree that death must come from primary involvement of the respiratory center. To quote from their own report: "It is suggested that the essential lesion of serum anaphylaxis is localized in the respiratory center."

Auer and Lewis disagree with these views and offer as evidence the fact that typical anaphylactic death can be induced in guinea pigs even after section of the vagi and sympathetic, thus showing that involvement of the respiratory center of the medulla is an unnecessary assumption in explaining the phenomenon.

The adherents to the colloidal theory of the nature of anaphylactic phenomena, among whom may be mentioned Zangger,[40] Novy[41] and others hold that the mechanism involved is simply one of colloidal displacement in the body plasma, no special localized area being assumed.

As stated above, the interpretation of Biedl and Kraus is in some ways the simplest and most convenient. They find that in dogs fall of blood pressure is a characteristic and constant result of reinjection, and, furthermore, that the fall in pressure parallels the progress of the symptoms. Accompanying this drop there is an increase in heart rate; this leaves open only one interpretation —the fall in pressure is the result of great peripheral vasodilation. It follows, therefore, that anaphylactic shock must express itself at least partly through vasodilation. Experiments made by stimulating both central and peripheral nervous system failed to bring about a rise of pressure, and adrenalin, which ordinarily causes great vasoconstriction, proved of very little or no aid; as this drug is known to act on the peripheral nervous apparatus in the vessel walls, it was concluded that the vasodilation of anaphylactic shock was due to the paralysis of the peripheral vasomotor apparatus. This explains why stimulation of either the vasomotor nerves or vasomotor center failed to produce a rise in pressure. A further proof of the probability of this view is found in the fact that if

barium chloride is administered before the second injection the blood pressure fall is avoided, and this salt is known to act directly on the smooth muscles of the vessel walls causing vasoconstriction. Having established the fact that the fall of pressure is a constant phenomenon in connection with anaphylaxis the authors conclude that the other symptoms are easily explained on this basis. Fall in pressure results in brain anemia, and as a direct consequence of the latter various symptoms of convulsion, paralysis, etc., are called out. However, this admirably convenient and simple conception fails to take into account the Auer and Lewis experiment of the cut vagi and sympathetics referred to above.

We have now considered the development of ideas concerning the nature of the phenomenon of serum toxicity, its relation to associated phenomena, its external and postmortem manifestations, and the ideas concerning the mechanism of symptom production. All that now remains is to discuss the theories as to the basic causes underlying these things.

Any discussion of the cause of a phenomenon must take into account the conditions met with and the influence they are likely to have on the final result. Von Eisler[39] has worked with the effect of salts and nonelectrolytes on lytic poisons and in the report of his work has given a rather comprehensive conception of the conditions and media in and through which a poison must act if it is to produce an effect. He holds that the permeability of membranes is closely associated with the toxic action of all substances. Such membranes being colloidal they are influenced by widely different factors, among which may be mentioned friction and temperature and the closely related factor of diffusion rate. Besides these, surface tension and the production of electrical potential must be considered.

In biological reactions we deal with colloids, crystalloids and electrolytes which are not independent but to a very large extent interactive and interdependent, and these substances in turn react with the highly complex structure of the cell plasma. The interaction of all these things is conditioned by, and dependent upon, the state of the colloids making up the cell membrane. From this statement of von Eisler it can readily be seen that the poisonous reaction of a serum may be a highly complicated process, a fact which it is well to bear in mind in considering the theories which various workers have advanced to account for serum toxicity.

The various theories of anaphylactic reactions and secondary serum toxicity can be grouped in two main classes. On the one hand we find a group of men who maintain that all the facts can be explained on the basis of physical or colloidal changes, and on the other we find a group that supports the idea of true poison involvement.

In the first volume of the *Zeitschrift für Immunitätsforschung* there appears an article by Zangger[40] in which immunity reactions are discussed from the standpoint of physical-colloidal changes. The following is a brief statement of the essential points brought out:

The substances entering into immunity reaction are colloids, and for this reason such reactions take place, not between homogeneous systems, but between colloidal systems. Thus colloids and colloidal reactions form the basis of the following changes: (1) separation processes such as precipitation and

agglutination, (2) processes of the opposite order, namely, lysis, solution, dispersion and increasing affinity of colloids for the media. The colloidal theory tries to explain the immunity and related reactions on the basis of these phenomena.

First of all the writer holds that the chemical view of the nature of these reactions is not justified, because the chemistry of the process is absolutely unknown at the present time and, as he says, without this a chemical theory is untenable, furthermore, to his mind, the chemical explanation does not cover all the facts.

The fundamental points of the colloidal theory are as follows:

1. The speed of a reaction is conditioned by the rate of passage between colloidal phases.

2. Equilibrium depends upon the distribution of the different phases, and upon the state and character of the limiting membrane.

3. The extent of the phases and the limiting membranes are of importance.

These laws are not only fundamental to the theory under consideration, but to the whole subject of colloidal reactions as well. This parallel is, therefore, taken as an argument in favor of the theory, and, furthermore, the laws known to govern the behavior of immune bodies under varying conditions of concentration and temperature, as well as those having to do with the influence of electrolytes, light, shaking, etc., seem to bear out this contention, at least to a certain extent.

From synthetic experiments the author also finds confirmation of his views. For instance, he finds that two colloids which independently have identical actions, when placed together do not combine their actions in the manner of a summation. In fact, one may actually neutralize the other. The degree of summation or neutralization depends on the relative concentration of the two substances. Besides this he finds that the course of such reactions is identical with that of immunity processes. Perhaps the most important of his synthetic colloid experiments are those in which he is able to substitute prepared colloids for the active substances in immunity reactions. Thus he says, "Known colloidal substances reproduce in many instances the scale of immunity reactions. Lipoids, particularly cholestrin in suspension in water, have an antitoxic action for toxins of such diverse origin as tetano toxin, tetano lysin, poison of bees, snakes, etc. Furthermore, many serums complemented with soaps give reaction characteristic of normal serums—heat liability, etc."

The scope of this theory, as well as its essential character, is given in the following classification of processes which he regards as being of purely colloidal nature:

1. Changes in membrane permeability, such as thickening, hardening, death due to alteration in substances transmitted, permeability resulting from the above, local destruction, such as opsonin action and phagocytosis, diffuse solution, such as lysis, etc.

2. Disturbances of cohesion—local destruction, dissolution of membrane, such as opsonin action and phagocytosis; solution, lysis.

The colloidal theory then, with its assumption of change in the physical state of membranes and plasma through disturbance and displacement of col-

loids, embraces all the phenomena of precipitation, agglutination, opsonin action, phagocytosis and lysis. The work of Novy and his associates which treats the phenomenon of anaphylaxis from the same angle, will now be considered.

The first observations were made in connection with anaphylatoxins and for these experiments agar, produced each time with definite technic, was used, since it was found that if physical conditions and the time element were not carefully taken into account the resulting product gave varying and unsatisfactory results. This agar suspension was incubated with rat serum and injected into a guinea pig and it was found that 0.25 c.c. killed. However, if this same substance was injected into a rat to the amount of 15 c.c., no poisonous action could be demonstrated. This latter point is of importance from the standpoint of the theory.

There was some reason to believe that by the incubation a ferment had been produced which was responsible for the action. To test this the serum was centrifuged and the clear homogeneous liquid was again injected, with the same result. This showed that if a ferment was present it must be a liquid, not a substance in solution. However, if such a ferment were present, progressive action in poison production should be noted and might be indicated by a fermentation curve. Successive toxicity tests brought out the surprising fact that toxicity did not steadily increase, but appeared and disappeared at regular intervals, first rising to a maximum and then falling off again to zero, the oscillations covering a period of about thirty minutes. Such a curve corresponds exactly with what is known as the colloidal periodicity curve. In the case of normal rabbit serum injected into guinea pigs, the significant observation was made that the addition of water tremendously increased the toxic action.

Since it was possible to produce a poison from agar in vitro the attempt was made to call forth the production of a similar poison in vivo. For some time attempts in this direction failed, but here, too, results were finally obtained, it simply being a question of getting the agar in the proper state before use. This experiment demonstrated beyond a doubt that anaphylactic shock could be produced in animals which had never been sensitized. This same phenomenon was shown by Vaughan in connection with his protein poison and may perhaps have a bearing on the subject of the primary toxicity of serums.

Probably the most striking outcome of these experiments was the production of nonspecific anaphylactic shock. The immune serum of a spirochete rat was applied to the organisms in low dilution (1:10) and agglutination took place. Later however, the organisms became active again. Tests were made with high dilutions (1:5000) and it was found that the organisms instantly showed great agitation and underwent almost immediate lysis. It seemed not improbable that some such phenomenon might be concerned in anaphylaxis. To test this out, a sensitized and a control animal were each injected with 14 c.c. of distilled water and it was found that the sensitized animal died of acute anaphylactic shock, while the normal animal showed no ill effects. This, then, constituted nonspecific anaphylactic shock, a phenomenon hitherto unknown. To confirm this result, attempts were made to reproduce the reaction in vitro, and these met with immediate success, as it was shown that poison

was produced from serum and distilled water in a powerful manner and at tremendous speed provided the dilutions were right.

The theory advanced to explain these results is as follows: Colloidal substances are born to function within certain limits. If anything is done to displace them permanently beyond their normal limits death follows. Thus Novy holds that proteins may exist in the aggregate, in colloidal suspension or in dispersion, and if a protein normally functioning in colloidal suspension is, for any reason, driven beyond the limits where a colloidal state is possible and remains there for any length of time, death results. A rebound to the first position usually takes place, and if this occurs before the animal has suffocated, recovery takes place. In such instances, moreover, there is often a secondary rebound shown in a secondary anaphylactic shock of a mild nature following the severe but nonfatal symptoms of the first. Such reactions are probably all in the direction of dispersion, and sensitization consists in a partial colloidal displacement which on the second injection is rendered complete.

Anaphylatoxin, then, is not a poison, but a physical state according to this view, and "it is possible to use anything under the sun and kill animals simply by altering the arrangement of the serum."

While the above views are maintained by some of the present workers, the majority hold to the idea that specific poisonous substances are involved. This conception of the phenomenon was really the first to be advanced, and like all other theories has gone through a series of evolutionary changes as a result of the addition of new facts from time to time.

One of the first theories in this connection, long since discarded, was that of Hamburger and Moro who supposed that the first injection called forth the production of precipitins and these on the second injection formed precipitates which interfered with the pulmonary circulation. This theory is in the same class with those advanced in connection with defibrinated blood transfer and falls to the ground principally because the symptoms produced are not of the type that might be expected from the presence of capillary emboli and furthermore no such emboli can be demonstrated.

The theory of Gay and Southard is of a different nature and, while not generally credited, still has its supporters. These observers briefly state their views as follows:

"It is clear that sensitization of guinea pigs to horse serum is associated with the persistence of an unneutralized portion of the serum in the sensitized animal and that the intoxication is due to some condition of the body cells which renders them particularly susceptible to those portions of the serum which have already been eliminated from the first dose."

In other words, a remnant of the first injection, "anaphylactin," remains in the blood of the sensitized animal, undigested and unchanged. This substance, which may be transferred from animal to animal, producing passive anaphylaxis, brings about a condition of hyperreceptivity or hypersusceptibility of the body cells for the homologous protein and on the second injection the violent interaction of these two factors causes the symptoms and death.

Richet thought that a substance in protein matter, "congestin," when injected into an animal called forth the formation of "toxogenin" in the animal

body. The second injection, carrying with it a second quantity of congestin, reacted with the toxogenin and produced a poison "apotoxin," which, acting essentially as a nerve poison, produced anaphylaxis. This theory is a close approximation to the more completely worked out and thoroughly understood theory of Vaughan and Wheeler, to be presented later. Whereas this theory imagines hypothetical and entirely unknown substances, that of the authors[42] mentioned presents fairly definite chemical groups which have not only been isolated, at least partly, but concerning whose chemical reaction many facts are known.

Bresredka thought that serum protein matter contained two substances which are active in producing anaphylaxis. During the period of incubation a substance called "sensibilogen" calls forth the production of "sensibilisin" by the body which at the time of the second injection reacts with the other protein substance, "antisensibilisin," to form a poison which acts in the central nervous system.

In 1909, Friedberger[43] advanced his theory of sessile receptors. He thought that at the first injection precipitins were formed which, not being produced in large quantities, remained attached to the cells as sessile precipitins. On the second injection these sessile precipitins were thought to react with the foreign proteins and produce anaphylaxis. The primary assumption of this theory of course was that a relationship existed between precipitins and anaphylaxis, a supposition which he explained by saying that the use of a large first injection caused the production of a large number of precipitins, of which some, from their very number, were detached from the cells and functioned as free precipitins. These free precipitins, he thought, were the cause of precipitate formation, whereas the sessile precipitins caused anaphylaxis. This interesting theory has been abandoned, partly on the ground of work done by its originator.

Two years later the same observer[44] found that by digesting precipitates with normal serum he was able to produce a powerful poison which he called "anaphylatoxin," a piece of work very similar to that of Friedmann in connection with blood corpuscle digestion. This poisonous substance was at once thought to be the true poison of anaphylaxis, and it seemed as though the problem of hypersensitization and anaphylaxis had been definitely solved. It soon became evident, however, that Friedberger's discovery had been credited with too wide a significance, for it was learned from the work of Bresredka and others that anaphylatoxins could be produced just as well from, for instance, starch and agar as from precipitates. This, of course, necessitated the discard of this theory as an explanation of anaphylaxis.

Perhaps the best known and most widely credited theory of anaphylaxis at the present time is that of Vaughan and Wheeler,[45] advanced in 1907, and differing from the Friedberger hypothesis, which it preceded by two years, in that it is based on known facts capable of chemical verification. These observers had found that by cleaving the protein molecule with dilute alkali in absolute alcohol they were able to separate a poisonous and a nonpoisonous part from proteins of the most diverse origin. The poisonous part was, as far as could be determined, identical in every case, whereas the nonpoisonous parts were not the same but proved to be characteristic of the particular protein from which

they were derived. This led to the conception that the protein molecule was made up of a nucleus or "archon" which was identical in all proteins and to which the secondary groups characteristic of each protein were attached.

Experiments made with the substances thus isolated gave interesting results. It was found that the injection of the poisonous part was highly fatal to experimental animals and that it killed with identical symptoms in all cases. Sensitization with this substance proved impossible and immunity could not be established. The nonpoisonous part gave rise on injection to phenomena of a wholly different order—it sensitized and was specific to the protein from which it had been derived, that is, it sensitized only to the homologous protein.

This, then, constituted a separation of sensitizing and anaphylactic substances, and demonstrated that the two substances were not identical. This had been suggested by previous observations and later work has brought additional confirmation. Thus Bresredka showed that serum heated to 50° to 60°C. lost its toxic property, but retained its ability to sensitize up to a temperature of 120°C.

Gay and Adler[46] separated the sensitizing and toxic portions by fractional precipitation with $(NH_4)_2\ SO_4$. One-third saturation gave the euglobulin fraction which was highly sensitizing but atoxic in its effect on animals, while the product from the two-thirds saturation gave a product which was at once sensitizing and toxic.

Kraus and Volk[47] found that heating serum at 100°C. for ten minutes destroyed the thermolabile toxic substance so that the serum was no longer able to produce anaphylactic shock, but the same serum was still able to sensitize.

The next step in the development of the theory was, of course, the investigation of these poisonous and nonpoisonous substances. This work was carried out with great thoroughness and a large number of reactions were worked out for both substances. Chief among these were the protein color reactions, though the nonpoisonous part was shown to respond to the Molisch test for carbohydrates. These researches left little room for doubt that the essential sensitizing and anaphylactic substances of serums were protein in nature, and this conclusion was indirectly substantiated by the positive and negative findings of other workers in the field.

Doer and Russ[48] concluded as a result of their studies in anaphylaxis that the sensitizing and toxic portions were associated with the globulins,—albumins, albumoses, and peptones being totally inactive.

Pick and Youmanouchi[49] obtained inconclusive results with serum lipoids as anaphylactogens. They found that single injections of such lipoids gave no sensitization, either active or passive, to subsequent injections of normal serum but that by repeated injections of normal serum both types could be produced.

The negative result of Sleeswijk[50] in attempting to establish the serum lipoids as the poisonous group responsible for anaphylaxis further strengthens Vaughan's[51] view. He worked with alcohol extracts of serum and found, to quote from his own report, that "serum lipoids are indifferent for sensitive animals. That portion of the serum which is insoluble in alcohol is practically without toxic effect and acts as a vaccine."

That the sensitizing and toxic groups are not identical can no longer be

doubted, but contrary to the views of most others, Vaughan and Wheeler deny that a mixed protein is necessary to produce the phenomena of anaphylaxis. They hold that the sensitizing and toxic portions are simply different groups of the same molecule, not actually separate substances.

These facts are the basis of the theory which follows—a theory whose consideration has been reserved until the last because it has suffered the least from adverse criticism and covers most of the points which others either fail to include or explain indefinitely and from pure hypothesis.

"In experimental anaphylaxis the first injection introduces into the body a foreign protein. This must be digested and the body cells slowly elaborate a specific proteolytic ferment which slowly digests it. In doing this certain body cells acquire a new function. The protein of the first injection is slowly digested, usually without the development of recognizable effects. . . . After the protein of the first injection has been disposed of, the new ferment in the form of a zymogen continues to be formed in the cells and on the second injection, after the proper interval, this zymogen is activated and splits up the protein so promptly and so abundantly that the liberated poison induces the symptoms of anaphylactic shock."

It is wholly beyond the scope and aim of this paper to distinguish between the two great schools of anaphylactic theory whose development and essential conceptions have been herewith outlined. The question has been and still is open, and further investigation alone can determine which is correct and tenable in the last analysis.

SUMMARY.

Serum toxicity, in its broadest sense, involves two types of phenomena,—primary toxicity and serum anaphylaxis.

Primary toxicity is due to a heat sensitive toxin independent of hemolysins, precipitins, agglutinins and anaphylactins.

In anaphylaxis the substance called forth by the parenteral injection of the sensitizing dose may under varied conditions act as an agglutinin, precipitin, lysin, or anaphylactin since it is probable that the same element is concerned in all cases.

The symptoms of anaphylaxis are practically identical in every case for animals of the same species. The symptoms vary in different species.

Reports on autopsy findings in cases of anaphylactic death do not wholly agree.

The mechanism of anaphylactic symptom production is still a matter of theory.

Two schools of thought as regards the theory of anaphylaxis exist at the present time: the physical colloidal theory, and the theories of true anaphylactin involvement. Each has its strong claims so that the question of which is correct is still open.

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CONCERNING THE CHEMISTRY OF PERNICIOUS ANEMIA

By Theodore L. Squier, Ann Arbor, Mich.

IDIOPATHIC pernicious anemia is by some considered essentially a disease of the gastrointestinal tract, involving atrophy of the mucosa and absorption either of enterogenous poisons or protein split products. By others it is considered a disease due to the hemolytic action of toxins elaborated in disease processes, and still others believe hypersplenism to be the causal factor.

Cederburg[1] holds that theoretically, at least, we can assume that by constant parenteral splitting of proteins and the entrance of split products into the blood stream a condition can arise which leads to a severe pernicious anemia. He calls attention to the similarity of the clinical findings in pernicious anemia with those of anaphylaxis and poisoning by protein split products. Assuming a constitutional weakness of the alimentary canal (constitutional predisposition of Schauman) a slight destructive process of the intestinal mucosa would be sufficient to break down the barricade against foreign proteins. A small amount of slightly changed protein could then pass into the blood stream and sensitize the organism against various foodstuffs. Eventually the individual becomes sensitized to practically all protein foods, so that after each meal partly changed albumoses pass through the mucosa, and are quickly broken down with liberation of protein poison. These split products have been shown to be not only hemolytic, but to act as a strong stimulus to the hematopoietic organs (Schittenhelm, Weichard und Grisshamer[2]). Furthermore, in protein poisoning or anaphylaxis, severe destruction of the intestinal mucosa has been observed by Schittenhelm and Weichard,[3] Richet,[4] Manwaring,[5] and Edmunds.[6] Having once become permeable, a vicious circle is instituted. The intestine permits increasingly large amounts of unbroken protein to leak through, with the result that there is an increasing liberation of protein poison and consequently greater hemolysis; marked stimulation of the bone marrow, and a pernicious anemia picture of progressively increasing severity. While Cederburg[1] regards the intestinal canal as perhaps the usual source of the protein products, he calls attention to the fact that in diseases of any kind where there is tissue and organ destruction an anemia can arise resembling in every respect the classic cryptogenic form. For example, the anemia of pregnancy is quite probably due to the liberation of protein split products. That protein poisons do play an active role in the disturbances accompanying pregnancy is an acknowledged fact. Eclampsia, for example, is undoubtedly due to anaphylaxis (Weichard[7]). The anemia of lues, of malaria, and of tuberculosis may all be attributed to the action of protein poisons liberated through tissue destruction. The presence of intestinal parasites such as uncinaria, tænia saginata and especially bothriocephalus latus may, where there is already a predisposition to weakness of the mucosa, suffice to set the anemic process in motion. Another causal (auslösender) factor of importance is chronic inflammation of the intestine which very quickly causes a mucosa already constitutionally weak to become permeable to incompletely digested proteins. Protracted or chronic

anaphylaxis leads, Cederburg thinks, to an antigen-antibody-complement reaction, whereby a very different poison is set free. Or, if one uses the terminology of Vaughan, a ferment is elaborated which tears down the foreign protein or substrate and liberates the toxic element. The poison acts indirectly: first through the liver and secondarily through the intestine (Manwaring[5]) in producing anemia. It must be assumed that in the portal system parenteral protein digestion occurs, and protein poison is here produced which exerts its hemolytic action on the red cells.

The peculiar remission periods are homologous, Cederburg[1] thinks, with the anallergic phenomena of anaphylaxis. After severe anaphylactic shock (clinically comparable to extreme intoxication) an animal is refractory for a certain period against the specific protein. The anallergic condition comes on suddenly and manifests itself as a blood crisis. Erythrocyte destruction ceases together with the attendant overstimulation of the hematopoietic organs. Consequently the bone marrow begins to exert its normal activity and the rapid improvement in the blood picture is made clear. Vaughan[8] regards the antianaphylactic state as due simply to the development of tolerance. To enter into a discussion of the theories regarding antianaphylaxis would carry us far beyond the scope of our subject. Whatever the actual mechanism of the process may be, the anallergic state passes once more into that of allergy and again the protein poison exerts its deleterious action. This cycle of remission and recidive repeats itself until the hematopoietic system is exhausted.

In connection with the subject of protein split products, some of the phenomena seen in pernicious anemia of horses are worthy of note. From the stomachs of horses suffering with the disease, larvæ of a fly (Œstridæ) have been obtained from whose bodies an exceedingly active thermostabile toxin, œstrin, has been isolated. Injection of œstrin into the blood of healthy horses causes an anemia resembling in all respects the typical horse pernicious anemia. If blood plasma from horses sick with the disease is injected into healthy ones, the infection is transmitted and pernicious anemia results. In this latter case, however, the poison element is thermolabile, and heating for one hour at 58° destroys its virulence. Seyderhelm[9, 10, 11, 12] found the so-called virus in the blood serum, urine and feces, but not in the sputum. Subcutaneous or intravenous injection of serum filtered through a Chamberland or Berkefeld filter and which yielded negative results upon microscopic and bacteriologic examination, when injected produced in every case the typical anemia, provided the subject was a horse or mule. Injections into other species of animals failed. It is certainly very plausible, theoretically, to regard the virus of Seyderhelm as serum containing a specific proteolytic ferment capable of liberating protein poison. Injection of the ferment containing serum passively sensitizes the horse against some protein which we must assume is one of the constituents of its own body since the phenomenon occurs only upon injection into a horse or mule. Vaughan[8] has shown that serum and organ extracts from sensitized animals are inactivated when heated to 56° for thirty minutes,—clearly harmonious with the thermolability of Seyderhelm's virus. Moffitt[13] has injected into horses human blood from cases of pernicious anemia with uniformly nega-

tive results as would be expected on the assumption of specific ferments as a causal agent. Mathes' assistant, Hunter, injected human blood from a pernicious anemic patient into a monkey and also obtained negative results (Mathes[65]). If injected into an anthrapoid ape or into man one might expect symptoms of pernicious anemia to result, but in a horse or monkey the negative results could be predicted.

HEMOLYTIC TOXINS AS THE CAUSE OF PERNICIOUS ANEMIA.

That pernicious anemia is the result of a hemolytic toxemia is a theory which has received much consideration. A large number of chemical substances such as œstrin, oleic acid, saponin, pyrodin, acetanilid, phenylhydrazin, nitrobenzol, β-imino-azolylethylbenzaldehyde, toluylendiamin, and p-oxyphenylethylamin are active hemolytic agents and injection of suitable doses will produce hemolysis with attendant hemoglobinuria and anemia. In connection with pernicious anemia those hemolytic poisons which arise during the course of digestion or by putrefaction in the intestine are of especial interest. Iwao[14] has been able to isolate p-oxyphenylethylamin from autolyzing pancreas, putrefying horse flesh, and Swiss cheese. It is quite evident that this base may normally arise in the intestine from putrefying food, and in fact Berthelot and Bertrand[15] have isolated from human intestinal contents an organism of the Friedländer pneumobacillus group which they have named B. aminophillus, and which is able to form p-oxyphenylethylamin from tyrosin. In fact even the colon bacillus may, under certain conditions, produce this base from tyrosin. Iwao[14] concludes that among the toxins of intestinal origin p-oxyphenylethylamin is one capable of markedly changing the blood properties, and which experimentally can produce in animals an anemia with a picture similar to that of pernicious anemia. Barger and Dale[16] have isolated another hemolytic amin, β-imino-azolylethylamin from the mucosa of the small intestine of an ox. This substance when injected causes hemolysis and a general picture of anaphylactic poisoning with the exception that there is probably no change in the clotting time of the blood. Biedl and Kraus[17] hold, however, that this poison does delay clotting. Mellanby and Twort[18] have shown that β-imino-azolylethylamin can be formed from histidin in the intestine by the action of a bacillus which will grow only in alkaline media. In absorption of such toxic amins is to be found a very plausible explanation for the origin of anemias. Grawitz,[19] on the same basis, held coprastasis an important factor in pernicious anemia, and believed that through reabsorption of toxic substances arising from increased protein decay a general destruction of erythrocytes may occur with a resulting progressive anemia. In many cases atrophy of the intestinal mucosa is present, and to a vicious circle resulting from the decreased digestive and assimilative power Grawitz attributes the progressive character of the disease. He suggests also the possibility of fetal toxins being absorbed in pregnancy and leading to the anemia sometimes seen in such cases. On the basis of experimental investigations in which he found no increase in either the soluble or fatty acids or ptomaines in the urine of patients sick with pernicious anemia, Bloch[20] contradicts Grawitz's theory regarding the toxic origin. Berger and Tsuchiya[21] investigated extracts obtained from the mucosa of animals sick with anemia

apparently identical with the idiopathic pernicious form, and they found such extracts to have a much stronger hemolytic power than extracts from the mucosa of normal animals. Ewald and Friedberger,[22] on the contrary, assert that extracts of the mucosa of such animals are no more hemolytic than normal.

Faust and Tallquist[23] demonstrated that in bothriocephalus infection anemia is due to oleic acid which in the form of cholesterol oleate is found in the proglottis of the parasite. In the host this salt is split and the free oleic acid liberated combines with alkalies of the blood and is absorbed as soap. Thus the acid enters the circulation where it exerts its harmful action on the erythrocytes while the cholesterin radicle passes out unchanged in the feces. Tallquist[24] points out that the hemolytic action appears only upon dissolution of the worm segments and concludes that possibly the active hemolysin is enclosed, so to speak, in an albumin covering which must be broken down before the toxin can be freed and reabsorbed. Why the parasite goes into solution in some cases and in others remains intact is a phenomenon which needs to be explained, and an explanation of this would at the same time make clear why some cases of bothriocephalus infection lead to anemia while others do not.

If pernicious anemia is produced by hemolytic toxins, it is not unnatural to expect that highly active hemolysins should be found in the bodies of patients dying from the disease. McPhedran[25] prepared extracts by mincing organs in alcohol and so treating the filtrate that in the end he obtained two fractions, the first containing in addition to simple glycerids and free fatty acids cholesterol and its esters if they were present, while the second fraction contained only acetone insoluble substances. In the majority of cases cholesterol and unsaponified matter was removed from the first fraction before testing. Upon comparing the hemolytic power of such organ extracts from cases of cancer of the prostate, pneumonia, secondary anemia, and idiopathic pernicious anemia, he found that the figures obtained in pernicious anemia fell entirely within the limits of those obtained in other conditions and gave evidence of the presence of none of the hemolytic toxins supposed to be present as the cause. From the liver in cases of acute yellow atrophy and phosphorous poisoning Joannovics and Pick[26] obtained fatty acids which were not only very active hemolysins, but could actually be demonstrated as present in the blood. They suggested, therefore, that the hemolytic effects of such liver extracts were due to the fatty acids produced. By the tissue destruction of the toxin these unsaturated fatty acids of the liver are freed from their normal lecithin-like combination and are in a sense activated. In toxic anemias in general these investigators[27] looked for the cause of the hemolysis in the fatty acids liberated from cells destroyed by the action of the poisonous principle. The toxins causing pernicious anemia, if toxins are the cause, may act in this same manner.

Closely associated with the view that the hemolytic activity of pernicious anemia is due to fatty acids is the theory that a general disturbance of the lipoid mechanism of the body is the primary cause of the disease. Chemical examination of the cortex of the adrenals in such cases shows it to be filled with lipoid material and especially cholesterin and its esters. It is quite probable that this tissue exerts an influence on metabolism through its cholesterin control. (Howell.[28]) Two

cases are cited by Kinnicutt[29] both of which at autopsy showed lipoidosis of the suprarenal cortex. In one case the degeneration was so complete that in places only fat infiltrated stroma remained. Hueck[30] has found that in pernicious anemia the lipoid content of the suprarenal cortex is increased. Landau[31] likewise found that there was a marked disturbance in the cortical tissue, and he thinks this of considerable significance because of the intimate relation which the cortex bears to the control of the cholesterol content of the blood.

The role played by the spleen in hemolytic processes is more or less uncertain, and the various views regarding its chemistry will be discussed in detail later. Moffitt[32] considers that a hypersplenic condition is brought about by toxins which reach the spleen through the lienal artery. Erythrolysis does not take place in the spleen, but in some way the erythrocytes are sensitized and prepared for later destruction in the liver, marrow, or lymph glands. Weidenreich noted that in pernicious anemia the lumen of the central artery of the spleen is so obliterated as to hinder the normal blood flow and force an unusually large amount of blood to travel by way of the capillaries directly into the pulp area. Once in contact with the connective tissue spaces of the pulp area, the erythrocyte is sensitized and marked for destruction. No attempt is made to explain this sensitization from its chemical or mechanical standpoint.

CHEMICAL CHANGES IN THE BLOOD.

In practically every case of pernicious anemia there is marked delay in the clotting time of the blood. This fact has been already mentioned in discussing the possible relation of pernicious anemia to anaphylactic phenomena. Drinker and Hurwitz[33] made a careful study of the factors of coagulation in pernicious anemia and determined quantitatively the different elements concerned in the phenomenon. They concluded from their investigations that prothrombin is diminished slightly in all cases, but that this diminution is not great and is unimportant provided active regeneration is in progress. Antithrombin and fibrinogen were found to be normal, even in the presence of a very low cell count. In one case in which there was pronounced diminution of prothrombin, the platelet counts were strikingly low. Hurwitz[34] has been able to show that fluctuations in the amount of prothrombin may be produced by substances affecting the number of platelets, and any toxin which produces a reduction in their number will simultaneously diminish the prothrombin of the circulating blood. No definite parallelism, however, has been established between bone marrow destruction, the number of blood platelets, and the amount of prothrombin. This suggests, therefore, that a reduction in the number of blood platelets alone will not cause a dangerous prothrombin deficiency; some other tissue must play a part in its formation. In his experimental aplastic anemias Hurwitz[34] found that the antithrombin and fibrinogen fluctuated but little from normal. Minot and Denny[35] agree in general with Hurwitz and Drinker's work, but found in two of their cases of pernicious anemia an increase rather than diminution in the prothrombin content. Furthermore, they found an abnormal antithrombin content while Hurwitz and Drinker did not. Moffitt[32] agrees with the authors cited regarding the diminution of blood platelets (and prothrombin) in pernicious anemia, and points out that splenectomy may be followed by a great increase in their number. Regarding the calcium

content of the blood, nothing is said, nor is mention made of any change in the viscosity.

The possible presence of specific proteolytic enzymes in the blood of individuals sick with pernicious anemia has already been mentioned in discussing anaphylactic phenomena as a hypothetical cause of the disease. The very evident indication of the existence of such enzymes in the blood of horses with pernicious anemia is especially worthy of note. No successful attempts, however, have been made thus far to demonstrate conclusively that similar ferments are present in human blood.

Ruttan and Adami[36] analyzed blood serum obtained at an autopsy performed five hours after death. They found the specific gravity to be 1.0261 which is below the figures cited by them as normal (1.027 to 1.030). Proteins made up 5.2 per cent by weight of the total substance, and of these 2.3 per cent represented the globulin, and the remaining 2.9 per cent, the serum albumin fractions. The ash was found to be 0.875 per cent or about 12½ per cent above the figure usually given. The total protein as found by these workers was accordingly about 40 per cent below normal while in addition the ratio of the globulins to the serum albumins was changed.

The fragility of the reds in pernicious anemia is altered through chemical changes in the cell envelope. McNeil[37] found that in varied groups of anemias the resistance of the reds to saponin hemolysis was diminished in all, and was most diminished in severe pernicious anemia. In chronic or less severe pernicious anemia the resistance is no more lessened than is cases of severe secondary anemia, and even in the worst cases of pernicious anemia the diminution is less than that which occurs in hemolytic jaundice. Saponin hemolysis is considered by McNeil[37] as a test of the cholesterin value of the cell envelope. Being antihemolytic the cholesterin content is an important factor in anemic conditions and its lack in pernicious anemia is thought by this worker to be a permanent and progressive defect.

In relation to fatty acids in the blood, one has to consider first whether in hemolytic diseases such as pernicious anemia fatty acids enter the blood in increased amount; and second, whether the amount of fatty acid entering the blood parallels the severity of the disease. King[38] found that in pernicious anemia there was an increase in the total fats of the blood, a decrease in the free cholesterin, and a strikingly high iodine number. His values for these constituents are as follows: Total fats, normal average, 5.600; pernicious anemia, 8.376; free cholesterin, normal average, 0.814; pernicious anemia, 0.342; iodine number, normal average, 90.00; pernicious anemia, 225.00. He concludes, therefore, that there is a definite parallelism between unsaturated fatty acids in the blood and hemolysis. This view is more or less opposed to the work of McPhedran[25] on the relation of fatty acids to pernicious anemia. McPhedran tested the hemolytic power of various fatty acids and found the lytic dose for ½ c.c. of normal washed red corpuscles to be as follows:

Sod. oleate,	.027 to .030 mg.
Sod. palmitate,	.40 mg.
Sod. linoleate,	.037 mg.
Sod. erucate,	.066 mg.

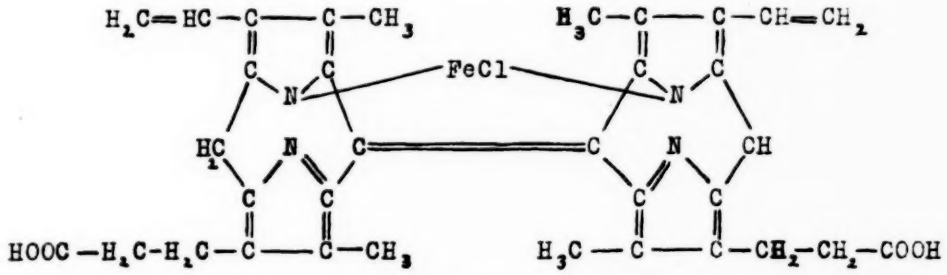
From these results it would appear that unsaturated fats with two or more double linked carbon atoms, as, for example, sodium linoleate are unable to cause any stronger hemolytic action than the simple double linked oleates, and McPhedran concludes, therefore, that hemolysis by fatty acids is not in proportion to the degree of unsaturation. In the blood of pernicious anemia patients the increase in total fats as shown by King was about 49 per cent while the increase in the iodine number was 127 per cent, indicating almost three times as high a degree of unsaturation. If this increase, as McPhedran believes, does not increase the hemolytic power, we must look to the decrease in free cholesterin for its cause. Lamar,[39] however, found that linoleic and linolenic acids in the form of Na salts were able to dissolve pneumococci more rapidly than did sodium oleate. Moreover, he found that the intensity of lytic action on the cocci varied directly with the degree of unsaturation, and accordingly he reached the conclusion that the hemolytic and bacteriolytic activity of the soaps of unsaturated fatty acids is probably due in part to their avidity for protein and not wholly to their lipolytic ability. Eppinger[40] likewise notes that in conditions associated with hemolysis, such as pernicious anemia and hemolytic icterus, there is an increase in the unsaturated fatty acids in the blood. The weight of evidence, therefore, indicates that the fatty acids are increased in the blood in pernicious anemia, but whether or not the increase parallels the severity of the anemia is still unclear.

HEMOLYSIS IN PERNICIOUS ANEMIA.

The hemolytic influence of foreign proteins, various poisons, fatty acids and lack of cholesterin has already been discussed. Here I wish to take up the question of the rate of destruction of erythrocytes as compared with the rate of regeneration, and the method of disposal of the products of hemolysis. The blood picture in pernicious anemia does not express the active processes going on, but merely indicates the mean,—the sum total of blood destroying factors set against the blood building factors. When the destructive factors are abnormally active, the hematopoietic organs are stimulated as has been already mentioned, and an attempt is made to counteract the loss. The actual amount of blood destruction is best determined by estimation of the secreted blood pigment. Schneider[41] believes that in the liver-spleen circulation the erythrocyte is disabled, that by contact with the spleen pulp it is in some way rendered more susceptible to hemolysis. Addis[42] considers that the influence of the spleen has something to do with cholesterin metabolism and attributes the change to activity of the peculiar endothelial phagocytic cells situated especially in the sinuses of the spleen, and to a less extent in the capillaries of lymph glands and bone marrow. The same type of cells stretching across the lumen of liver capillaries form the Kupffer or stellate cells of the liver.

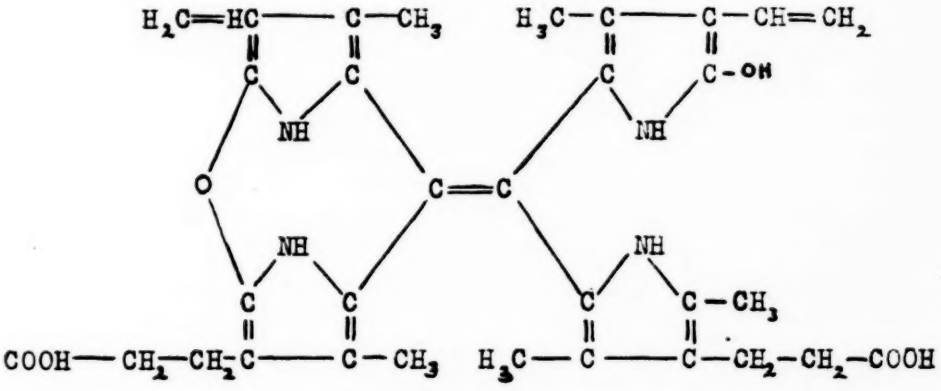
The first step in hemoglobin pigment decomposition is the liberation of hemoglobin from the worn-out or damaged erythrocyte. Addis[42] remarks that the special function of the Kupffer cells is not only to phagocytose the red blood cells but to take up extruded hemoglobin as well, and droplets of hemoglobin have been seen by him passing from the Kupffer cells into the cells of the liver. In the liver cells the second step takes place and the hemochromogen of hemo-

globin is separated from the globin fraction. Outside the body this separation can be effected by treating hemoglobin with hydrochloric acid, hemin being formed. The structural formula as given by Addis[42] for hemin is as follows:



Hemin

The mechanism of the subsequent process is not yet understood, but in some way the hemoglobin pigment is transformed by the liver cells into bilirubin. The extent of change can be seen by comparing the formula for hemin with that for bilirubin:



Bilirubin

It will be noticed that iron has gone out from the molecule and the oxygen content is increased. That hemoglobin pigment does give rise to bilirubin Addis demonstrated by injecting hemoglobin pigment into the blood stream. An almost quantitative increase in the bilirubin excreted in the bile followed. For our purpose it will suffice to briefly sketch the subsequent steps in hemoglobin metabolism. After entering the intestine, bilirubin is reduced to urobilinogen. This is assumed to be absorbed in part from the intestine and polymerized into a hypothetical urobilin complex which is normally removed by the liver. The surest indication of generalized disturbance of the liver function is based according to Addis on a determination of the extent of failure of synthesis of hemoglobin pigment from this urobilin complex. Where active erythrocyte destruction is going on, it is natural to expect that the limit must be approached above which the liver can no longer dispose of the liberated pigment. That such actually is the case has been shown by Sellards and Minot.[43] These workers

found that compared with normal, less hemoglobin is required to produce hemoglobinuria in patients in whom there is increased blood destruction as, e.g., in pernicious anemia. In secondary anemia there is, as a rule, no excessive blood destruction and the hemoglobin necessary to produce hemoglobinuria in these cases approached normal. The amount of hemoglobin necessary to cause hemoglobinuria bears no relation to the red count, but is in direct proportion to the amount of blood destruction taking place. This last, providing complicating factors are absent, is directly proportional to the excretion of urobilin in the intestine. Eppinger[40] found that the normal urobilinogen execretion was 0.12 to 0.15 grams per day, while in pernicious anemia the excretion was 0.24 to 1.14 grams per day. Schneider[41] estimated the amount of hemolysis by examination of duodenal contents and found in pernicious anemia excessive excretion of bile pigments or pleochromie, and urobilinocholia. Pleochromie is an expression of immediate hemolysis and in pernicious anemia whether in crisis or remission is a constant finding. Urobilinocholia indicates a heaping up of pigment in the portal system and varies directly as the portal system is surcharged or becomes relatively empty of the plus of pigment. Regardless of whether or not gross liver changes can be demonstrated, urobilinocholia is highest in crisis. Schneider[41] points out that anemia caused by gastrointestinal hemorrhage, and in which the blood picture simulates that of pernicious anemia will definitely show an absence of pleochromia and urobilinocholia upon duodenal estimation of the bile pigments.

THE METABOLISM IN PERNICIOUS ANEMIA.

To Meyer and DuBois[44] is due the most valuable contribution on the basal metabolism in pernicious anemia, and their results will here be briefly reviewed. Five cases were studied in all of which there was an increased metabolism varying from 2 per cent to 33 per cent above the normal average. There are no profound qualitative metabolic changes in pernicious anemia as shown by the relationship between the CO_2 produced and the O_2 consumed, and fats and carbohydrates are burned to the same end products as in health. Clearly then, a reduction of hemoglobin does not preclude the possibility of either a normal or even an augmented metabolism. Normally the O_2 supply to the tissues is beyond the immediate requirements, and in anemia, since there is no means of augmenting the O_2 carrying capacity per unit of blood, the margin of safety from asphyxiation must be encroached upon with the result that the blood returns to the heart in various degrees of asphyxia. Plesch[45] has called attention to the fact that in anemia there is an increased heart rate. This suffices in uncomplicated cases to compensate for the increased demands per unit of blood in spite of the greatly diminishd hemoglobin content. Morawitz[46] accounts for the increased O_2 consumption and CO_2 production in pernicious anemia by the presence of the nucleated reds whose O_2 needs are extremely high. Meyer and DuBois[44] conclude that there are some grounds for the belief that the height of metabolism is a measure of the severity of the clinical picture. Peabody and Wentworth[47] found no change in the vital capacity of the lungs in pernicious anemia.

IRON METABOLISM IN PERNICIOUS ANEMIA.

The importance of iron as a constituent of hemoglobin makes it a factor of much interest in the study of anemias. Whether an iron lack plays any role in pernicious anemia, and if so whether the feeding of preparations containing iron will be of any therapeutic value have been widely discussed questions. In chlorosis the therapeutic value of iron has long been acknowledged, but Morawitz[46] believes its value here to lie not in its effect upon the blood forming organs, but rather upon some other focus of disturbance, leading only secondarily to an increase in hemoglobin. Müller[48] concluded that inorganic iron salts added to an iron free diet in anemic animals increased erythrogenesis. Tartakowsky[49] held the same view. Abderhalden[50] also pointed out that inorganic iron as well as hemoglobin or hematin added to a diet poor in iron increased hemoglobin formation, but to a less extent than occurred when a diet of iron rich food was given. He concludes that whatever be the form in which iron is administered, it is absorbed by the same channels, stored in the same organs, and eliminated by the same routes, and he furthermore suggests that in all probability all iron assimilated, whatever its original source, is taken from the digestive tract in an ionized state. Hauserman[51] fed anemic animals on a low iron diet with $FeCl_2$ added, another group he fed on a low iron diet only, while a third group received food poor in iron but with hemoglobin added, and a fourth group were fed a mixed diet of iron-containing foods. His results showed that $FeCl_2$ was not an available source for iron to be changed to hemoglobin. Asher and Grossenbacher[52] found that after splenectomy in dogs there was a marked increase in the iron elimination. They concluded, therefore, that the spleen is an important organ in intermediary iron metabolism enabling the body to conserve and neutralize its supply. Austin and Pearce[53] obtained conflicting results and decided that there was no good evidence to support the view that the spleen exercised any fundamental influence on iron metabolism. Muir and Dunn[54] investigated iron retention in the organs in cases of hemolytic anemia using chiefly in their experiments guinea pigs made anemic by repeated injections of antiserum from a goat sensitized against guinea pig's corpuscles. The normal iron content of the organs in a 200 gram pig was as follows:

Liver,	4.64 mg.
Kidney,	0.54 mg.
Spleen,	0.24 mg.
Total,	5.46 mg.

In anemic animals the average percentage of iron in the liver and kidneys was about five times normal, and in the spleen it was about three times normal. In 200 gram severely anemic pigs the iron content was—

Liver,	25.02 mg.
Kidney,	3.69 mg.
Spleen,	2.49 mg.

Unless hemoglobin is present in the urine practically no increase of iron can be demonstrated in the kidneys, and the amount of hemoglobin escaping in the urine is roughly proportional to the amount of iron deposited. Muir and Dunn[54] emphasize the fact that a broad distinction can be made between the hemosiderin

deposits resulting from lysis and those resulting from phagocytosis of reds. In the former the iron deposit first appears in the cells of the peripheral zone of the liver lobule, and from thence spreads inward, giving at first a diffuse blue reaction, but later, beginning first at the periphery, granules of hemosiderin occur. In phagocytosis, on the contrary, the hemosideric deposits bear no special relation to the periphery, but occur rather throughout the liver lobules.

CHEMISTRY OF THE SPLEEN IN PERNICIOUS ANEMIA.

The spleen is supposed to exert a marked influence on iron metabolism. The increase in iron elimination seen by Asher and Grossenbacher[52] after splenectomy has already been mentioned, but is rather hard to understand. Certainly most workers have obtained contrary results. Pepper and Austin[55] found that in pernicious anemia the iron output through the feces, although never above normal, showed a decrease of 40 per cent after operation; while before splenectomy the excretion of urobilinogen and urobilin was about three times normal, the output two months after splenectomy was reduced to one-seventh of that before the operation. With reference to nitrogen they found that a slight positive balance before splenectomy was followed by retention fourteen days postoperative with a return to the preoperative balance after one month. The uric acid output showed a decrease of 22 per cent after the operation although it never exceeded normal limits. That the spleen is an important factor in blood destruction is evident from the decreased urobilin output following splenectomy. Pibram[56] points out that stasis of blood in the spleen, e. g., in chronic passive congestion, is associated with increased erythrolysis, and that urobilinuria can be induced by splenic congestion. Furthermore the blood crisis after splenectomy indicates either that the bone marrow has been stimulated to greater activity or that some inhibitory factor has been removed. The theory that bone marrow stimulation has occurred is supported by the increased number of platelets seen after splenectomy. On the other hand Klemperer believes that the spleen elaborates an inhibiting hormone for bone marrow. However, experiments made by Krumbhaar[57] demonstrated that fresh splenic extracts stimulated rather than inhibited the bone marrow, and furthermore Pearce and Pepper[58] have pointed out that the bone marrow activity does not begin until several months have elapsed after splenectomy. Krumbhaar[59] has indicated that it is difficult to prove that the lessened hemolysis after splenectomy is due to the absence of the spleen for neither normal spleens nor those removed in operation can be shown to possess any increased hemolytic activity. Furthermore analyses of blood entering and leaving the spleen have failed to throw any light on this subject. (Krumbhaar and Musser.[57]) After splenectomy the hemolytic resistance of the reds is increased, and this may be one of the factors leading to improvement after operation. Pearce and Karsner[60] found that splenectomy in normal animals was followed by an increased resistance of erythrocytes. Pearce, Austin and Evans[61] also found the resistance increased, while Joannòvics and Pick[62] have shown in experimental animals that if the spleen is removed a much larger dose than normal of toluylenediamine is required to produce anemia. Joannovics[63] made a fistula between the splenic vein and the left renal vein and in this way diverted the splenic blood into the inferior vena cava. Animals so treated were able to

tolerate toluylenediamine much better than could normal animals. He concluded that normally toluylenediamine to a slight extent but the spleen to a very much greater extent plays the active role in blood destruction. The decomposition products from the erythrocytes are, according to Joannovics,[63] taken out by the spleen and sent on to the liver through the portal vein. In this way an overabundance of material for the manufacture of bile pigment is at hand, and as a result the liver produces an excessive amount of concentrated bile. This leads to stasis, reabsorption and icterus. Krumbhaar[59] points out that whatever may be the cause for the improvement after splenectomy, the subsequent relapse is probably due to other organs such as the hemolymph nodes, accessory spleens and Kupffer liver cells, taking over the function of the spleen, but as yet no positive evidence has been produced to substantiate this theory. Splenectomy is not always followed by a decrease in the urobilin output. Robertson calls attention to the fact that those cases in which the urobilin excretion before splenectomy was high and which after the operation exhibited only a transient reduction or none at all did not show so much improvement in other respects as did those cases in which the urobilin output was permanently reduced.

Eppinger,[40] as already has been noted, asserts that in pernicious anemia and similar conditions the unsaturated fatty acids of the blood are increased. Splenectomy serves not only to reduce the unsaturated fatty acid content, but it also increases the cholesterol and total fat content of the blood. King[38] believes that the occurrence of highly unsaturated fatty acids is in some way intimately dependent upon the activity of the spleen, for he found that following splenectomy the iodine number of the fats of the blood is reduced and the production of icterus by hemolytic agents is made more difficult.

The most evident feature of the chemical pathology of the liver in pernicious anemia is the enormous deposits of hemosiderin which occur (Hunter[64]), and this fact substantiates the view that the hemolytic action takes place in the portal circulation. If the reverse were true, or if hemolysis occurred both in the portal and general circulation, one would expect to find iron deposits in the spleen increased, but such is not the case. (Mathes,[65] Hunter.[64]) The difference in the character of the deposits resulting from lysis and phagocytosis has been mentioned. (Muir and Dunn.[54]) That the Kupffer cells of the liver are in a state of increased erythrocyte phagocytosis in pernicious anemia has been shown by Moffitt.[32]

THE KIDNEYS IN PERNICIOUS ANEMIA.

But little work has been done with reference to the kidney chemistry in pernicious anemia. Thus far an abstract of a paper read by Christian[66] at Peter Bent Brigham Hospital is practically the only source of information on this phase of the subject. The phenolsulphonephthalein output even in severe cases was found to be normal, indicating no excretory insufficiency. If the urine of normal individuals who are receiving three meals a day is tested at intervals of two hours, decided variations in the volume and in the amount of solids present will be found. From figures thus obtained a curve may be plotted the contour of which is decidedly jagged (picket fence curve). In diseases of the kidneys the ability to vary the specific gravity and the output of various constituents is

diminished, in consequence whereof the curve loses its jagged appearance and flattens out. In pernicious anemia the specific gravity curves thus plotted become almost straight lines, while the curves of nitrogen elimination likewise show flattening, but to a less marked degree. Such curves point to the presence of functional kidney disturbances quite similar to those of chronic nephritis, and the appearance is fairly constant from day to day. After transfusion the functional curves become slightly more irregular. Pathologically the kidneys show no signs of nephritis. An increase in iron pigment, chiefly in the convoluted tubules, is about the only finding of note. Christian is working at present on the functional kidney curves obtained in pernicious anemia after various modes of treatment such as transfusion, splenectomy, arsenic, salvarsan, etc., and his results will doubtless be of much interest and value. The urine in pernicious anemia is usually of low specific gravity, and is pale from diminished pigment.[67]

GASTROINTESTINAL CONDITIONS IN PERNICIOUS ANEMIA.

Gastrointestinal disturbances are of peculiar interest in pernicious anemia for alimentary disorders have been and still are by many, considered the primary cause of the disease. Hunter,[64] as has been previously mentioned, regards the disease as an infection due to a specific glossitis, oral, gastric and intestinal sepsis. Stern[68] emphasizes the fact that periodically a soreness of the tongue and gums is noted, which is of importance from a diagnostic standpoint as one of the earliest symptoms. Mathes[65] also considers changes in the oral mucosa one of the earliest symptoms. Osler[67] says that pyorrhea alveolaris is found in every case of pernicious anemia. No special chemical agent is given as the cause for this condition, and indeed aside from the many references to stomatitis, little mention of the mouth is made.

In the stomach an absence of free HCl is a constant finding, so constant in fact, that in anemias where free HCl is present the pernicious type is ruled out. The combined acid also is extraordinarily low, being seldom over 10 in severe cases and more often it does not exceed 5. The achlorhydria in itself signifies faulty gastric digestion since pepsin is unable to act save in slightly acid media, but apparently in the majority of cases there is in addition more or less complete achylia gastrica. The significance of these conditions is a subject much debated. On the basis of postmortem and clinical observations von Nothnagel[69] concluded that the alimentary disturbance was the fundamental cause of pernicious anemia. Lewy[70] and Fenwick[71] agree with this view. On the contrary Baur and Weigle have advocated that the intestinal destruction is brought about by changes in the blood. Nolen[73] has reported two cases of pernicious anemia in which atrophy of the mucosa was present, and Quincke,[74] Henry and Osler,[75] and Brabazon[76] have each reported one case with similar gastric findings. Brabazon's case was not substantiated by microscopic examination. Kinnicutt,[29] in 1878, reported two cases of pernicious anemia both of which were autopsied. The stomach wall where it came in contact with the fluid contents of the stomach was in both cases thinner than normal. Microscopical examinations were made of sections from various regions of the stomach wall, and in selecting material care was used to obtain tissue which had not been in long contact with the gastric fluids.

Extensive areas of mucosa were found in which not a trace of gastric tubules could be seen. In some places, especially in the pyloric zone, remnants of tubules were found. A peculiar hyaline material was also seen taking in places the shape of the tubules and forming hyaline casts. In both cases there was a general dense small-cell-infiltration of the mucosa such as is seen in inflammatory processes. That the atrophy was not due to postmortem effects is indicated by the fact that the more superficial parts of the glandular structure were least involved; greatest destruction took place in the deeper tissues. Kinnicutt[29] believed that the dense small-cell infiltration certainly could not be regarded as the result of impaired nutrition, and that in his cases at least this process strongly pointed to a dependence of atrophy upon an inflammatory process. He concluded that as a result of inflammation a primary atrophy of the gastric mucosa occurs, and that in this lesion is to be found an explanation of certain cases of pernicious anemia. Strausz[72] speaks of the coincidence of apepsia gastrica and pernicious anemia and holds that certain relations must exist between the disease and abnormal conditions of the intestinal mucosa. Some of the more recent autopsy findings apparently show that the mucosa is unaltered both in the stomach and in the intestine. Faber and Bloch[81, 82] found that providing postmortem changes are avoided by injection of formaldehyde, atrophic changes of the gastric and intestinal mucosæ in pernicious anemia are often absent or slight. R. von Lippman[77] autopsied a case of pernicious anemia that clinically showed achylia gastrica. Especial care was used to guard against postmortem changes (the intestine was removed one hour after death), and in this case no evidences of atrophy of the mucosa and nothing of note, save extreme anemia of tissues, was found. Consequently he agrees that unless autopsy is quickly performed findings with reference to the mucosa in such cases are of little value. Whatever the pathological findings in such cases may be, it is certainly true that there are very marked alterations of the gastric secretions. The apparent lack of pepsin and inactivity of the acid-secreting glands seen clinically are rather hard to explain in the light of the normality of the mucosa claimed to have been found at autopsy. Whether or not normal peptic secretion goes on and the uniform lack of digestive ability is due to an antienzyme of some sort is a question well worth investigation. It must be borne in mind that the presence of NaCl, carbohydrates, and the products of protein digestion all tend to inhibit peptic activity.

Concerning the condition of the pancreatic-intestinal enzymes and hormones no information is afforded by the literature. Probably they are able to compensate for the digestive inability of the stomach, for were this not the case much more serious alimentary disturbances would be present than are usually found.

EXPERIMENTAL ANEMIAS.

We propose here not to enter into a detailed discussion of experimental anemias in general, but rather to enumerate a few of the methods by which anemias with a blood picture resembling that of pernicious anemia have been produced. Preeminent in this group is the experimental pernicious anemia produced by Seyderhelm[9] in healthy horses by the injection of filtered serum from a horse sick with the disease. The possibility of homologous sensitization in this case has already been discussed. Kumagai[78] showed that the erythrocytes of

sensitized animals upon second injection with the specific protein are less resistant to destructive agents of various kinds than is normally the case. Against saponin, however, he found the resistant force unchanged. Schittenhelm, Weichard and Grisshamer[2] have shown that in artificial poisoning the hematopoietic organs are stimulated to great activity. Protein split products have the same stimulating effect and cause megaloblasts and megalocytes to appear in the peripheral blood in large numbers. The reduced erythrocyte resistance together with the bone marrow stimulation combine to give a picture very closely resembling in many cases idiopathic pernicious anemia. Schlecht and Schwenker[79] injected adrenalin in dogs and found that this drug caused a decrease in the number of reds, a decrease in the eosinophiles, and a decrease in the total hemoglobin content. Iwao[14] by repeated subcutaneous injections of p-oxyphenylethylamin was able to produce in guinea pigs an anemia with the characteristics of pernicious anemia both with respect to the blood picture and course; the number of erythrocytes and the total hemoglobin content were markedly reduced, while the hemoglobin content of the individual reds was relatively high. Poikilocytosis and polychromatophilia both occurred to a low degree, and both normoblasts and macrocytes were found. The number of eosinophiles was reduced, but there was a relatively high lymphocyte count. Iwao[14] compares the physiological action of p-oxyphenylethylamin with adrenalin in that both cause a rise in blood pressure due to the effect on the smooth muscle fibers. We have already discussed the intestinal source of this poison and pointed out the possibility of its being an etiological factor in pernicious anemia.

Buting[80] produced anemia in rabbits by the injection of ricin. After injection of the drug there was a leucopenia followed by leucocytosis, pyknosis and karyolysis as a rule. The red cells showed marked hemolysis indicated by hemoglobinuria and pigment accumulations in the spleen pulp, liver and lymph glands. Nucleated reds appeared in the peripheral blood stream, and their number depended first on the amount of toxin injected, and secondly, on the condition of the erythrogenetic tissue of the marrow. Buting's attempts to produce chronic anemia with ricin were only partially successful, because tolerance to the drug was rapidly established. In those cases in which the rabbits remained partially susceptible, an anemia was eventually produced with a blood picture identical with pernicious anemia and entirely different from that seen in the secondary anemia following hemorrhage. With saponin it was much easier to produce a chronic anemia since tolerance to it is less readily established. A reduction of the red count, nucleated reds in the blood stream, and pigment accumulations in the organs were all seen as was the case with ricin. Autopsy of animals rendered anemic in this way showed partial depletion of the mature bone marrow cells and necrosis of the remainder. There was marrow sclerosis together with diffuse hemorrhage. The liver showed central necrosis of the lobules together with marked turgescence of the veins and capillaries. From these findings Buting[80] concludes that the bone marrow throws nucleated reds into the circulation only when the mature erythrocytes at the periphery of the erythrogenetic center are destroyed by some toxin or depleted by hemorrhage. If there is extensive bone marrow injury, the groups of blood forming cells may be almost completely

replaced by scar tissue in which case the spleen becomes hematopoietic, and blood cells are formed in its sinuses. Unless large amounts of toxin are quickly thrown into the circulation, the bone marrow is uninjured; e. g., upon subcutaneous injection of ricin or saponin absorption is so slow that the toxin is saturated by cells in the circulation with resulting erythrolysis and the cells of the bone marrow are consequently uninjured.

SUMMARY AND CONCLUSIONS.

1. Pernicious anemia may be considered the result of a gastrointestinal disturbance leading to destruction of mucosa sufficient either to allow undigested proteins to leak through into the blood stream where their parenteral digestion liberates protein poisons, or to the absorption of known hemolytic toxins produced in the course of intestinal putrefaction such as, e. g., p-oxyphenylethylamin. In either case the poison has a destructive influence on the intestinal mucosa, as well as the more evident hemolytic effect, and this results in the establishment of a vicious circle.

2. Others consider the disease to be the result of some change in the lipoid metabolism whereby large amounts of unsaturated fatty acids such as oleic are liberated.

3. Hypersplenism is a third explanation given as a possible cause for pernicious anemia. Stasis or occlusion of the splenic artery causes congestion of the sinus spaces and those erythrocytes which come in contact with the parenchyma are so changed as to be marked for destruction.

4. The clotting ability of blood in pernicious anemia is reduced, probably as a result of a reduction in the number of platelets.

5. There is an extreme oligocythemia and reduction in the total volume of blood. The hemoglobin content of the individual cells is relatively high.

6. The erythrocytes in pernicious anemia are more susceptible to such hemolytic agents as saponin. This is probably a result of the decrease in the cholesterin content of the cell envelope.

7. Specific proteolytic ferments may be present in the blood as appears to be the case in pernicious anemia of horses, and homologous sensitization, at least in the case of this animal, is possible.

8. The severity of the anemic blood picture is an expression of the difference in the rate of regeneration set against the rate of red cell destruction.

9. The only efficient method for determining the rate of destruction lies in quantitative estimations of pigment production, and this is best carried out by examination of the duodenal contents.

10. The basal metabolism is increased in pernicious anemia because of the excessive oxygen needs of nucleated reds. In spite of the low oxygen carrying ability per unit of blood, compensation may be effected by an increased heart rate and volume output.

11. Iron is deposited in large amounts in the liver, spleen, lymph glands, and to some extent in the kidney. The comparatively enormous deposits of iron in the liver indicate that erythrolysis occurs in the portal circulation.

12. Splenectomy lessens the severity of the disease by increasing the resistance of the reds to hemolytic agents. When the hemolymph glands and accessory spleens take on the splenic function a relapse occurs.

13. Liver changes are characterized chiefly by enormous deposits of hemosiderin.

14. Except in cases where there is hemoglobinuria, iron deposits in the kidney are slight and the amount of iron deposited is roughly proportional to the degree of hemoglobinuria.

15. In all cases of pernicious anemia there is achlorhydria, and in a large majority of cases achylia gastrica as well. Autopsies have given conflicting results as to the condition of the mucosa, and the apparent deficiency of enzymes may be due to the presence of inhibiting substances. This, however, is improbable.

16. By injections of hemolysins, such as saponin, experimental anemias can be produced in animals that are apparently identical both in the blood picture and course with true idiopathic pernicious anemia.

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A REPORT OF TWO CASES OF FATAL HEROIN POISONING*

By Wm. D. McNally, A.B., Chicago.

IN a review of the literature, I found reported only one case of fatal heroin poisoning,[1] with a possible second case in which the heroin was mixed with antipyrine. Poisoning with heroin, which did not produce death, is reported by Glasgow.[2] A woman 34 years old, took .05 gram of heroin hydrochloride. After twenty minutes she complained of a severe headache, and cramps extending to the lower extremities. The pulse was 100 to 110 and regular. The eyes were wide open, with a fixed staring gaze, and reacted to light. She was restless for two hours, and talked as if out of her right mind. Most of the symptoms were those of morphine poisoning. The poisoning reported by Trawick,[3] from a hypodermic injection of 1/12 grain, caused, a few minutes later, an irregular respiration, and the pulse almost ceased. The patient had the appearance of a person profoundly under the influence of an opiate, but recovered after the administration of strychnine, salt solution, and artificial respiration. In the report of Weinzieher,[4] a woman slept for 52 hours after taking .01 gram of heroin. The symptoms reported by Soles,[5] after a woman had taken .167 gram of heroin, were as follows: myosis, slow pulse (40), subnormal temperature, and cramps in the extremities. In a case of poisoning reported by Comar and Buvat[6] 2.8 grams was consumed in twenty-four hours by a patient resulting in a high degree of nervousness, feeble-mindedness, and a general wretched condition. The heart and kidneys were less active than normally. Harnack[7] claims that heroin is more poisonous to man than to animals, giving a lengthy discussion of the pharmacology of heroin. Dreser[8] found that the lethal dose for rabbits was 100 times the therapeutic dose, codein ten times the therapeutic dose; in other words, for rabbits codein is more toxic than heroin.‡ The pharmacological and therapeutical literature is voluminous, and it is only within the last five years that heroin has become of toxicological interest.

Case No. 1.—There has been opportunity for me to study material of a case of heroin poisoning, entered to the service of Dr. Goldsmith, Ward 22, of the Cook County Hospital. W. K., age 20 years, a salesman, was admitted in an unconscious condition, and died seven hours later. The physical examination was comparatively negative save for coolness of the body, a blue mottling of the abdomen and a weak and irregular heart. The pupils were contracted. The pulmotor was used for intervals of three-quarters and one-half hours respectively. The stomach was washed out with permanganate solution. The respirations were very slow being 13 per minute on admission to the hospital and after the first use of the pulmotor were 42. They fell down to 16 when the pulmotor was used again. Just before death they were 19 per minute. From the postmortem examination, (Dr. E. R. Le Count) the following anatomic diagnosis was reached: The pupils of the eyes were equal and dilated, the external surface of the brain presented no change. Upon sectioning the pons, medulla, and cerebellar hemispheres no gross alterations or evidence of disease was noted. There was an engorgement of the abdominal veins and marked

*From Cook County Coroner's Laboratory, Chicago, Ill.

‡Dreser found 0.1 gram of heroin and 0.1 gram of codein to be the lethal doses for rabbits. The conclusion derived was based on the therapeutic dose of heroin .001 gram, and the therapeutic dose of codein .01 gram. Using these values, he obtained .10 : .001=100 for heroin. 0.10 : .01=10 for codein.

passive hyperemia and edema of the lungs; petechial hemorrhages in the epicardium and in the lining of the greater antrum of the stomach; dilatation of the mitral ring; persistent lymphoid tissue in the thymic body; hyperplasia of the lymph nodes in the spleen, of the lymph glands, of the solitary follicles of the stomach, small and large bowel, and of the Peyer's patches; hyperplasia of the aorta; slight chronic catarrhal prostatitis; left obliterative fibrous pleuritis. In an examination of the urine, (made by Prof. W. S. Haines for Dr. E. R. Le Count), albumin and sugar were found to be present in considerable quantities.

The results of the chemical examination of the organs are shown in Tables I and II.

TABLE I.

LAB. NO.	ORGAN	WEIGHT IN GRAMS	WT. USED IN GRAMS	ALKALOID FOUND IN GRAMS	TOTAL ALKALOID FOUND IN GRAMS
259	Brain	1236	200	None	None
260	Stomach contents	454	200	.0414	.0939
261	Intestines	1315	200	.0163	.1071
262	Liver	1480	171	.0018	.0155
263	Intestinal contents	1020	300	.0020	.0068
264	Kidney	125.5	100	.0007	.0009
265	Spleen	190	190	Trace	Trace
266	Stomach	349	120	.0256	.0744
267	Preservative on 261, 263, and 266	2250	300	None	None
268	Preservative on Kidney, Liver and Spleen	1040	200	.0007	.0036
					.3022

The alkaloid extracted from the liver, kidney, spleen, the preservative in which these organs were held, the intestines, and intestinal contents gave all the reactions for morphine. The alkaloid extracted from the stomach and stomach contents responded to the tests for heroin.

Case No. 2.—Mr. L. D., age 32, entered the service of Dr. Portis, Ward No. 24, of the Cook County Hospital, May 25, 1913. A transcript taken from the clinical record gave the following:

Patient in a comatose condition, respiration slow and grouped over periods of one and one-half minutes, with intervening periods of dyspnea lasting over one minute. Body of patient cold. Skin is dry and lobes of ears are cyanotic. Pulse is slow, small, regular, and soft. Pupils are pinpoint, conjunctivæ injected. No paralysis. Lips, mouth, and throat are negative. Heart normal, abdomen lax, no dullness. Extremities flaccid, reflexes present. From the postmortem examination (Dr. E. R. Le Count) the following anatomic diagnosis was made:

Passive hyperemia of the lungs, of the brain, and of the retroesophageal tissues; marked edema of the lungs, jejunum and ileum; marginal emphysema of the lungs; slight hyperplasia of the spleen. The lungs did not collapse when the pleural cavities, containing a large amount of fluid, were opened. The pulmonary artery and its branches were empty. The heart was loose and flabby. The inner surface of the calvarium was of a bluish gray. A large amount of cerebrospinal fluid was present, being very abundant in the sulci of the vertex of the brain where the convolutions are widely separated. There were no alterations in the fourth ventricle. On the surfaces made by sectioning the brain in the usual way, there was no gross disease. The blood from the heart gave a strongly positive Wassermann reaction.

A portion of the intestines, stomach, and stomach contents were submitted to me for examination. An analysis showed that the alkaloid heroin had been taken by the deceased. The examination was not as thorough as in the first case, because the material obtained was not as abundant. The chemical examination, results of which are shown in Table II, indicates that heroin can be recovered from the stomach and stomach contents unchanged. The Stas-Otto process was used in extracting the alkaloid from the tissues in the two cases reported.

TABLE II.

LAB. NO.	ORGAN	WEIGHT IN GRAMS	WT. USED IN GRAMS	ALKALOID FOUND IN GRAMS	TOTAL ALKALOID
393	Intestines	806	200	.0034	.0137
394	Preservative on 393 and 395	1036	300	.0008	.0027
395	Stomach	281.4	200	.0153	.0215
396	Stomach contents	47.0	47.	.0057	.0057
					.0436

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LABORATORY METHODS

ANIMAL INOCULATIONS SUPPLEMENTARY TO AN INTRODUCTORY COURSE IN PATHOGENIC BACTERIOLOGY*

By W. H. Manwaring, M.D., and John T. Connell, B.S.,
Stanford University, Calif.

THE essential feature of the introductory course in Pathogenic Bacteriology in Leland Stanford Junior University is the inclusion among the required student exercises of numerous animal inoculations and immunizations, together with introductory exercises in aseptic surgical technic. A weekly program of the course is given in Schedule I; the inoculations, immunizations, etc., in Schedule II.

The equipment for these exercises consists of four small rooms, in easy access to the microscopical laboratory, serving as: animal room, autopsy room, inoculation room, and operating room. The cost of animals, feed, etc., is about $5 per student, the students working in groups of two.

No objection to this work has been made by local antivivisectionists.

Schedule I. Weekly Program.

1st week—Media, air colonies, plating.
2nd week—Molds, yeasts, chromogens.
3rd week—Saprophytic, putrefactive.
4th week—Disinfectants, biological defenses.
5th week—Animal diseases.
6th week—Pyogenic, subpyogenic.
7th week—Anaerobes, toxemias.
8th week—Spirilla.
9th week—Midsemester practical examination.
10th week—Typhoid, dysentery.
11th week—Colon, enteritis (mixture of unknown).
12th week—Acid-fast, higher bacteria, blastomycetes.
13th week—Spirochetes, protozoa.
14th week—Final practical examination (includes at least one autopsy).

Schedule II. Inoculations, Immunizations, Autopsies, Etc.

3rd Week.

METHODS OF INOCULATION, TESTS OF COMMON SAPROPHYTES.

Tuesday.—Each group to inoculate four animals with pure cultures obtained from water, milk, decaying vegetable and animal matter, etc.

1. *Rabbit:* Intravenously, 2 c.c. 24 hr. broth, No. 1.
2. *Guinea Pig:* Intraperitoneally, 1 c.c. 24 hr. broth, No. 2.
3. *Pigeon:* Intramuscularly, 1 c.c. 24 hr. broth, No. 3.
4. *Rat:* Subcutaneously, 0.5 c.c. 24 hr. broth, No. 4.

Note clinical symptoms daily for two weeks. No autopsies.

BACTERIAL DISTRIBUTION, NORMAL ANIMAL BODY.

Thursday.—5. *Large Rabbit:* Etherize; with aseptic precautions ligate: (i) trachea, immediately above clavicle, (ii) trachea, immediately below larynx, (iii) esophagus, middle of

*Presented before the Pedagogical Section, Society of American Bacteriologists, New Haven, Conn., Dec. 28, 1916.

neck. Wash out with sterile NaCl-Sol.: (a) trachea, below ligatures, (b) trachea, between ligatures, (c) trachea, above ligatures, (d) pharynx, (e) esophagus, above ligature, (f) pleural cavity, (g) peritoneal cavity. With capillary pipettes draw samples of: (h) heart-blood, (i) bile, (j) urine, (k) gastric contents, (l) duodenal contents, and (m) contents of large intestine. Plate out one loopful of each sample thus obtained.

4th Week.

BIOLOGICAL DEFENSES.

MONDAY.—6. *Rabbit:* Draw 10 c.c. blood, aseptic precautions, carotid artery. Allow blood to coagulate, store in ice chest overnight. On Tuesday study bactericidal power (B. typhosus) of: (a) serum, (b) heated serum (60° C., 30 min.).

TUESDAY.—7. *Rabbit:* Kill by blow on back of neck, open abdomen, aseptic precautions, aspirate bile, and urine. Remove stomach contents, moisten with sterile salt-solution, centrifuge free from undigested food material. Test bactericidal power (B. typhosus) of: (c) urine, (d) bile, (e) gastric fluid.

WEDNESDAY.—8. *Large Rabbit:* Inject, late in afternoon, 10 c.c. 5% aleuronat into each pleural cavity. On Thursday kill rabbit by blow on back of neck, exsanguinate from carotid, open abdomen, aseptic precautions, and aspirate pleural exudate through diaphragm. Make smears, stain by Wright's method. Defibrinate, mix one sample with bacteria or spores (oral directions), incubate, make smears at end of 15 min., 30 min., and 1 hour.

5th Week.

INTRODUCTION TO PATHOGENICITY, AUTOPSY TECHNIC.

MONDAY.—9. *Guinea Pig:* Subcutaneously, 1 loopful 48 hr. broth, B. anthracis. Note clinical symptoms daily. Expect autopsy Wednesday. Plate out heart blood. Identify recovered microorganism. Make smears from heart blood, liver, spleen, and kidney. Histological sections will be made for you.

10. *Pigeon:* Intramuscularly, same dose, B. anthracis. Follow clinical symptoms daily for one week. No autopsy.

11. *Male Guinea Pig:* Intraperitoneally, 1 c.c. 48 hr. broth, B. mallei. Note clinical symptoms daily for 10 days. No autopsy.

THURSDAY.—12. *Rabbit, Guinea Pig, or Pigeon:* Subcutaneously, 1/10 loopful 24 hr. broth, B. pleurisepticus. Expect autopsy Friday. Recover and identify microorganism from heart blood. Make smears from heart blood, liver, spleen, and kidney.

FRIDAY.—Inoculate three flasks, special broth, B. diphtheriæ (Park No. 8). Incubate 10 days.

6th Week.

PYOGENIC, SUBPYOGENIC.

MONDAY.—13. *Rabbit:* Intravenously, 1/20 c.c. 48 hr. broth, S. aureus. Note clinical symptoms daily. Expect autopsy in about four days. If animal does not die, etherize on Friday. Plate out heart blood, and material from abnormal areas in heart muscle, kidney, etc. Make smears from abnormal areas. Histological sections will be made for you.

14. *Rabbit:* Subcutaneously, 1/4 c.c. 24 hr. $CaCO_3$ broth, S. pneumoniæ. Expect autopsy Tuesday. Recover and identify microorganism from heart blood, using special media. Make smears from heart blood, liver, kidney, and spleen.

WEDNESDAY.—15. *Small Rabbit:* Intraperitoneally, 4 c.c. mixed sputum. Expect autopsy Thursday. Plate out heart blood, using special blood-agar. Identify microorganisms isolated.

7th Week.

TOXEMIAS, ANAEROBES.

MONDAY.—Filter one special 10-day culture B. diphtheriæ. Test sterility of filtrate.

TUESDAY.—Centrifuge and wash the bacilli in one special 10-day culture B. diphtheriæ. Suspend washed microorganisms in original volume, physiological saline.

16. 250 gm. *Guinea Pig:* Subcutaneously, 1/4 c.c. special 10-day culture, B. diphtheriæ.

17. 250 gm. *Guinea Pig:* Subcutaneously ¼ c.c. special 10-day culture, B. diphtheriæ; followed by 1/10 c.c. diphtheria antitoxin, intraperitoneally.

18. 250 gm. *Guinea Pig:* Subcutaneously ¼ c.c. filtrate, from same culture.

19. 250 gm. *Guinea Pig:* Subcutaneously ¼ c.c. suspension, washed B. diphtheriæ. Note clinical symptoms daily for 7 days. If animals die, make Loeffler's blood serum cultures from heart blood, and site of injection. Note conditions of internal organs, particularly the adrenals, stomach and peritoneal surfaces.

20. *Guinea Pig:* Subcutaneously, ¼ c.c. 24 hr. broth, B. edematis. Note general and local symptoms daily. If death results, make smears from local lesions, liver, and heart blood.

8th Week.

SPIRILLA.

TUESDAY.—21. *Pigeon:* Intramuscularly, 1 c.c. 24 hr. broth, S. cholerae.

22. *Pigeon:* Intramuscularly, 1 c.c. 24 hr. broth, S. metchnikovii. If death results, isolate and identify microorganisms from heart blood. Make smears from heart blood and site of inoculation.

6th-10th Week.

AGGLUTINATING SERA.

23. *Rabbit:* Six repeated injections, three to five day intervals, 1 c.c. 24 hr. broth, B. typhosus or B. dysenteriæ. Make first two injections subcutaneously with killed cultures (60° C., 1 hr.); second two intraperitoneally, and last two intravenously with living cultures. Eight to ten days after the last injection draw serum, carotid artery, aseptic precautions. Determine: titer, specificity.

7th-12th Week.

TUBERCULOSIS.

24. *Guinea Pig:* Intraperitoneally, 1 c.c. suspension, B. tuberculosis.

25. *Guinea Pig:* Intraperitoneally, 1 c.c. tuberculous sputum. Keep animal in special cage. Examine twice weekly. Etherize about four weeks later. Histological sections will be made for you.

10th-11th Week.

ANAPHYLACTIC REACTION.

26, 27. 200 gm. *Guinea Pigs:* Subcutaneously, 1/40 c.c. goat serum: Test guinea pigs 14 to 18 days later, 3 c.c. goat serum, injected through ball of hind foot. Make similar injection into a normal control. If animals die, open thorax and determine condition of lungs.

10th-13th Week.

HEMOLYSIS.

28. *Rabbit:* Four repeated injections, three to five day intervals 1 c.c. 25% suspension goat corpuscles (suspensions will be prepared for you). Draw serum, marginal vein, eight to ten days after the last injection. Test: Inactivation, reactivation with guinea pig complement.

13th Week.

TRYPANOSOMES, SPIROCHETES.

MONDAY.—29. *White Rat:* Subcutaneously, ¼ c.c. rat's blood, T. lewisi.

30. *White Rat:* Subcutaneously, ¼ c.c. rat's blood, S. recurrens.

Examine blood daily. Make smears at height of infection. No autopsy.

4th-12th Week.

ASEPTIC SURGICAL TECHNIC.

31, 32. *Large Rabbits:* Each group to do two laparotomies. Among the operations recommended are: (a) Nephrectomy; (b) Splenectomy; (c) Ligation of inferior vena cava.

NOTE ON TECHNIC WITH FRIDERICIA APPARATUS

BY MILES J. BREUER, M.D., LINCOLN, NEB.

IN the *Journal of Laboratory and Clinical Medicine*, April, 1916, appears a description by J. J. R. Macleod of the apparatus and technic for determining the alveolar CO_2 by the Fridericia method. In following this technic, I was impressed with a considerable variation in the results of determinations in close succession and on the same person, on myself for instance. The inaccuracy was traced to the following cause. After the enclosed air is shaken with the

alkali, being shut in at both ends by the stopcocks, Macleod's directions read that the stopcock B should be turned into such a position that the water in which the apparatus is immersed, will run into the graduated tube. (This would actually be the position of Fig. III, and not that of Fig. II as stated there, the latter being probably a typographical error.)

When the stopcock B is turned into such a position, so that the water will run up into the graduated portion, it will usually carry with it a bubble of air, which has been held inside the stopcock. When the surplus alkali is allowed to run out, the stopcock is emptied, and as it is turned off, the air is enclosed in it. Then, when the water runs up into the graduated portion, the bubble is carried with it. This is obviated by the following modification of the technic as given by Macleod.

After shaking up the enclosed air with the alkali, immerse the apparatus up to the stopcock A in a cylinder of water, and turn the stopcock into position as shown in Fig. II, so that the water will run first into the ungraduated side of the instrument, filling the interior of the stopcock with water. Then the stopcock is turned into the position shown in Fig. III, so that the graduated side communicates with the water outside.

With this change in the technic, I have been able to obtain very consistent and accurate results.

CYANIDE POISONING IN A CASE OF TYPHOID FEVER

By Ludvig Hektoen, M.D., Walter S. Haines, M.D., and Victor C. Vaughan, M.D.

THIS report concerns a man, about 30 years old, previously in good health, who was in the early stages of typhoid fever and receiving the usual treatment. At 3:30 P.M. on the second or third day after he had taken to bed he received a particular capsule, which there is reason to believe contained potassium cyanide, and about half an hour later he was seized with a convulsion and became unconscious. The details are given below as taken from the nurse's chart.

Time.		Temp.	Pulse.	Resp.	Notes.
Dec. 5, 1	A.M.	102.8	99	..	
" " 3	"	102.6	98	..	
" " 6	"	101.4	98	..	Slept 2½ hours during night.
" " 9½	"	99.8	78	..	
" " 12	M.	100.8	80	..	
" " 2¾	P.M.	103.4	96	22	
" " 3½	"	....	..	..	Receives a particular capsule; vomits a little; at 4 o'clock he is seized with a convulsion and becomes unconscious; the arms are bent and drawn up, the hands clenched, the legs rigid, the eyes open and staring, the jaws locked, the face pale and somewhat cyanosed, and a peculiar humming sound is produced in the throat. The pulse weak and fluttering. Digitalin gr. $\frac{1}{100}$ and strychnine gr. $\frac{1}{40}$ and nitroglycerine gr. $\frac{1}{100}$.

Time.	Temp.	Pulse.	Resp.	Notes.
Dec. 5, 4¾ P.M.	104.2	132	..	Patient quieter.
" " 5¼ "	103.4	120	..	⅛ gr. morphine hypodermically.
" " 6¾ "	102.6	108	11	⅛ gr. morphine again.
" " 7¾ "	101.8	106	16	
" " 8¾ "	102.	104	..	Still rigid; morphine gr. ⅛ hypodermically.
" " 9¾ "	101.6	104	18	Seems more relaxed.
" " 10¾ "	101.8	106	16	
" " 11¾ "	102.6	108	..	Strychnine gr. 1/100 hypodermically.
Dec. 6, 12¾ A.M.	102.6	104	16	
" " 1¾ "	103.4	108	18	Arms and legs rigid.
" " 2¾ "	103.4	108	16	Morphine gr. ⅛ hypodermically.
" " 3¾ "	104.4	108	16	
" " 4½ "	....	..	..	Morphine gr. ⅛, strychnine gr. 1/40 hypodermically.
" " 5¾ "	105.	112	12	Respirations shallow.
" " 7 "	105.6	134	16	Rigid; jerks arms and legs at intervals.
" " 7¾ "	104.6	120	12	Morphine gr. ⅛, strychnine gr. 1/40 hypodermically.
" " 8½ "	105.2	138	..	
" " 10½ "	106.6	140	26	
" " 11½ "	105.6	136	24	
" " 12¼ P.M.	106.	140	32	Respiration shallow.
" " 1 "	106.	144	30	Leucocytes 3-4000 per c.mm.
" " 2 "	....	..	..	Delirious; nitroglycerine 1/100 gr.
Dec. 6, 2¾ P.M.	107.8	Uncountable.	56	
" " 3¾ "	106.5	"	45	
" " 4 "	....	..	..	A particular capsule.
" " 4½ "	106.2	150	38	
" " 5¼ "	104.6	148	30	Very restless.
" " 7 "	104.2	140	48	Convulsion—Death.

Soon after death the body was injected with a fluid containing formaldehyde and placed in a vault. The postmortem examination was made 23 days later. The body was in an excellent state of preservation and there was what was regarded as "some superficial bruises of the skin of the legs." There was well marked swelling of Peyer's patches and lymph follicles in the small intestines, most marked nearest the ileocecal valve. The spleen was enlarged and deep red in color. The liver was normal in size and showed on microscopic examination many typical areas of focal necrosis. The right chest cavity was obliterated by firm adhesions and the posterior parts of the lower lobes of both lungs were deeply congested and in part solid. The pia of the brain was congested. All the other organs appeared to be normal.

The chemical analysis (by Haines and Vaughan) gave small amounts of strychnine in the contents of the stomach and in the liver and definite indications of cyanide in the stomach contents.

Of the symptoms of cyanide poisoning, the slowing of the respiration observed for some hours after the first convulsion is highly significant.

IMPROVED TEST FOR INDICAN IN URINE*

By Fritz C. Askenstedt, M.D., Louisville, Ky.

THE clinical significance of indicanuria is still a subject of much confusion largely because the clinical tests for indican in common use are unreliable. This will be made apparent by even a brief consideration of the chemical changes to which indican is subject during the performance of the tests. By oxidation two molecules of the colorless indican ($C_8H_7NSO_4$) are converted into one of indigo-blue ($C_{16}H_{10}N_2O_2$) which by further exposure to oxygen is as readily reduced to the reddish yellow isatin ($C_8H_5NO_2$). Since the estimation of indican is always made on the amount of blue color obtained after indican has been converted into indigo-blue, it is of utmost importance to the accuracy of the test that all of the indican present be converted to indigo-blue, and that this, as soon as formed, shall be protected from further oxidation. Chloroform, in which indigo but not indican is soluble, serves to protect the indigo-blue from further chemical action. While the ordinary tests for indican are based on the above fundamental facts, grossly inaccurate estimates very often result from misuse or neglect of the following technical points:

1. *Proper Selection and Use of Oxidizing Agent.*—Even with the most thorough mixing of the oxidizing agent with the urine, the oxidation of all the molecules of indican contained in the urine does not take place simultaneously but progresses quantitatively, which renders the molecules of indigo-blue first formed liable to conversion into isatin before all the indican has been oxidized. The rapidity with which these processes of oxidation occurs depends upon the energy of the oxidizing agent, its concentration, and the temperature of the mixture. It is apparent that with an energetic oxidizer, such as potassium permanganate, the changes are much less under control than when a less energetic substance, as ferric sesquichloride, is employed. The practice of adding a few drops of a solution of potassium permanganate to a mixture of urine and hydrochloric acid has been found a faulty technic, because in addition to the disadvantages of an energetic oxidizer, there is, at least for a moment, an uneven distribution of the oxidizer, thereby overcharging a part of the urine, with the result of rapid isatin formation. An oxidizing agent of only moderate energy and with the largest possible surface of distribution is, therefore, to be preferred.

2. *Temperature.*—An objection to a low grade oxidizer, as the perchloride of iron, is the prolonged shaking with chloroform for extraction of the indigo, made necessary by the tardy action of the reagent. The simple direction to shake the mixture a few times and then set it aside for precipitation of the chloroform is entirely inadequate. The necessary duration of this process of extraction with chloroform is a serious objection to a general adoption and correct usage

*For helpful suggestions in the development of the tests for indican I wish to acknowledge indebtedness to Dr. Clifford Mitchell, of Chicago.

of such a reagent, but the period of shaking can be materially shortened by raising the temperature of the urine to 130 to 140 degrees F. When the permanganate is to be used, warming the urine simply increases the perplexities.

3. *Extraction of Indigo.*—Chloroform seems the most satisfactory agent. It should be added to the urine and well mixed with it before the oxidizer is added, to insure immediate extraction of the molecules of indigo first formed. Chloroform is capable of holding only a small amount of indigo in solution, and therefore soon becomes saturated when shaken with a mixture rich in this ingredient. A common fault of most clinical tests for indican is that the quantity of chloroform added is too small, and, as has already been intimated, the duration of the extraction of indigo entirely too short. These two defects can not be too strongly emphasized.

4. *Concentration of Urine.*—Practically all urines contain indican. The detection of indican is, therefore, of no more value than the revealed presence of urea or phosphates. Qualitative tests for such normal ingredients of the urine are of value only if standardized for a definite concentration, as well as quantity, of urine. A reaction that is normal to a urine of a specific gravity of 1020, may prove decidedly abnormal to a urine of 1010. A uniform concentration or dilution of the urines to be tested is accordingly a prerequisite to a practical qualitative test for indican.

5. *Contaminating Substances.*—It has been positively demonstrated that certain gases in the laboratory, notably formaldehyde, interfere with the conversion of indican to indigo. For this reason the laboratory should be properly ventilated and all utensils duly cleansed before using.

The qualitative test for indican described below is a simplified procedure of the writer's quantitative test published in the *New York Medical Journal,* June, 1912, and is offered to those practitioners who can not afford the twelve minutes necessary for a quantitative determination.

Dilute the urine until it has a sp. gr. of 1005. For example, if urine shows a sp. gr. of 1017, dilute five parts of urine with twelve parts of water; if its sp. gr. is 1021, dilute five parts of the urine with sixteen parts of water, etc., corrections being made for temperature. An exception is made for diabetic urine, which is diluted until its urea content is 0.5 per cent. Place 10 c.c. of the diluted urine in a test tube and warm over a flame until the lower end of the tube begins to feel hot to the hand. Then add 8 c.c. chloroform and mix by shaking a few times. Ten cubic centimeters of a solution of 0.4 per cent perchloride of iron in concentrated hydrochloric acid (Obermeyer's reagent) is now added, and, with the tube duly stoppered, quickly extract the indigo by shaking the tube two minutes, holding it in a horizontal position. By releasing the stopper once or twice during the procedure, squirting will be prevented. After this, let the chloroform fall to the bottom of the tube, then pour off most of the supernatant fluid, fill the tube nearly full with water, invert it a few times to wash the chloroform, and let it again precipitate in the tube. If indican is normal in amount, the chloroform will remain white or show a mere trace of blue. Any increase in blue exhibits a proportionate excess of indican. The

reading should be made as soon as the chloroform is precipitated, for on standing, the chloroform slowly becomes transparent, with an increase in the shade of blue when present.

Years of experimentation have demonstrated the accuracy and clinical value of this test.

THE DIAGNOSIS OF MALIGNANT TUMORS BY PARAFFIN SECTIONS OF CENTRIFUGED EXUDATES*

By F. S. Mandlebaum, M.D., New York City.

As an aid in the identification of tumor cells or minute fragments of tumor tissue in pleural or ascitic fluids, an examination of the sediment by the histological methods employed in routine tissue work has given excellent results for many years and has supplanted the examination of stained smears prepared from the fresh sediment.

Briefly stated, the technic of this simple method is the following:

1. The sediment is obtained in large conical tubes by means of the centrifuge. A small quantity of fluid may prove sufficient, but where large amounts have been aspirated at least 500 c.c. should be centrifuged.

2. Carefully decant the supernatant fluid, or better still, remove the fluid with a pipette and large rubber bulb.

3. Cover the sediment with a deep layer of 10 per cent formalin which must be added by means of a pipette or gently poured into the tube to avoid disturbing the sediment.

4. After six to twelve hours, depending upon the amount of sediment, carefully remove the formalin and replace by alcohol 95 per cent for twenty-four hours.

5. Remove the disc of fixed and hardened sediment by means of a thin knife blade. Transfer through absolute alcohol and chloroform into paraffin in the usual manner, trimming down the block if necessary.

6. Cut, mount and stain sections as in routine histological examinations.‡

Microscopic examination of the sections obtained by this simple procedure reveals tumor cells when present, or even tiny fragments of tumor tissue sufficient to establish the diagnosis of a malignant growth. If stained smears made from the fresh sediment are compared with the sections, the advantages of the method just described are apparent.

An accurate diagnosis of malignant tumors of the lung and pleura or of abdominal organs accompanied by ascites has been made by this method in a considerable number of cases, the diagnosis being confirmed subsequently by the clinical picture or by autopsy. A detailed account of these cases with the significance of budding cells, mitotic figures and other cytologic criteria is in preparation.

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*From the Pathological Department, Mount Sinai Hospital, New York City.

‡Several years ago, in the examination of a case of actinomycosis, the writer succeeded in obtaining excellent sections from a drop of pus which was fixed in formalin and embedded in celloidin: Proc. New York Path. Soc., 1901, 178.

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Editor-in-Chief: VICTOR C. VAUGHAN, M.D.
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EDITORIALS

The National Research Council

THE National Academy of Science was chartered by Congress in 1863, and it is the only scientific body in this country possessed of a Congressional charter. In this charter it was stated that one of the purposes of this organization would be to advise Congress and the President concerning scientific matters. From its foundation up to recent times, Congressional Committees occasionally consulted the Academy concerning scientific subjects. When Mr. Wilson became President, there were vacancies in three scientific bureaus and he asked the National Academy of Science to nominate men for these positions. This was done, and the appointments were made from the nominees. In April, 1916, President Wilson asked the National Academy of Science to appoint a committee, to be known as the National Research Council, whose chief function would be to encourage scientific research in this country, and to advise the Government concerning scientific needs. In accordance with this request, the Council was appointed and held its first meeting in September, 1916. The Council numbers more than forty, and the work since the first general meeting has been done by an Executive Committee of ten. The men on this Committee have served without financial recompense, have met twice a month, with

occasional extra meetings, and have attempted to correlate the scientific work in educational institutions, in special research laboratories, and in industrial science. Special committees have been appointed to undertake this work in different departments of science.

The rapid approach of war has led the Council to concentrate its efforts upon war problems. While the Council covers the whole field of science, we are specially interested in that part of it concerned with medicine and hygiene. Among the problems that have been formulated, and at which men are now at work, we may mention the following:

1. *Antitoxins.*—There are ten or twelve commercial firms preparing diphtheria and tetanus antitoxins. Under the present law, all of these are working under the supervision of the Public Health Service. All manufacturers of biological products must be licensed by the Federal Government, and the license is issued only after inspection. Besides this, the Public Health Service goes on to the market at least once a month, buys these antitoxins, and ascertains experimentally whether or not they come up to standard. It seems that we can rely upon commercial houses to supply diphtheria and tetanus antitoxins. In this connection it is well to know that the British Army surgeons have come to the conclusion that the protective dose of tetanus antitoxin need not exceed five hundred units.

Flexner, in charge of the Rockefeller Institute, has undertaken to become responsible for the preparation and supply of serums for the treatment of pneumonia, dysentery, and meningitis. Experience on the Texas border has shown that the serum prepared in the Rockefeller Institute for the treatment of pneumonia of type No. 1 is highly efficient. The data concerning the efficiency of dysentery serums are not altogether satisfactory. There has been more or less dysentery—much more than there should have been—on the Texas border. Flexner has undertaken the responsibility of the preparation and supply of this serum. In this connection, it may be well to state that Dakin reports that Dale has prepared a mixture of emetin with bismuth iodide which may be given by the mouth and which has proved of marked service in dysentery.

Major Craig has found that the commercial serum obtainable is not reliable in the treatment of meningitis. Fifty per cent of the cases of this disease treated with this serum ended fatally. On the other hand, of ten cases treated with the Flexner serum, only one died, and this man was practically moribund when received at the hospital. Flexner has agreed to take the responsibility for the preparation and supply of this serum.

2. *Vaccines.*—McCoy of the Hygienic Laboratory will take the responsibility of securing from commercial houses and testing smallpox vaccine. Some important researches on various points connected with smallpox vaccination are being carried out in the University of California. Special attention is being given there to the intradermal method. This produces only a small pustule, thus decreasing the probability of dangerous infection, and at the same time seems to give complete immunity. The possibility of using the purified vaccine of Noguchi is being investigated.

There seems to be good reason for having all the typhoid vaccine prepared in one laboratory and under one direction. This secures uniformity. Colonel Arthur, in charge of the Army Medical Corps in Washington, reports that the laboratory of that school will be prepared to furnish enough typhoid vaccine to vaccinate five million men as fast as they can be enlisted. Information from our allies in Europe concerning polyvalent vaccines is being sought.

3. *Poisonous Gases.*—Several chemists are already at work collecting material already known, and making further investigations concerning the best methods of neutralizing the poisonous gases that have been used in the European war. The gases which have been most used are chlorine, bromine, hydrocyanic, carbon monoxide, and an arsenical gas.

4. *Excreta.*—Major Craig thinks that while, on the whole, methods of disposal of excreta at present in use in our Army are satisfactory, improvement can be made. In permanent and semi-permanent camps incinerators give good results. The possibility of mixing some chemical with the fecal matter in order to hasten its destruction is under consideration.

5. *Drinking Water.*—There seems to be no difficulty in securing safe water in the large camps. The Lyster hypochloride bag has been used on the border and on the incursion into Mexico, and has proved quite satisfactory. There is much need, however, of some tablet or ampul which the soldier may carry and which he may drop into his canteen when he is compelled to fill it from doubtful or unknown sources. There have been many cases of dysentery in Mexico and along the Texas border due to taking water from doubtful sources, especially when men are on scout duty, or when, for any reason, they are not within reach of the general water supply of the camp. It is expected that valuable information will be secured along this line from those who have been in Europe.

6. *Rations.*—It seems to be the general opinion among army medical men that the present ration is well balanced and is satisfactory. We understand that in the Mesopotamian campaign compressed yeast has been issued in order to supply vitamins. It has been suggested that since cranberries keep so easily, there might be a ration containing this valuable and delectable ingredient. The whole question of the food supply of the nation and its distribution is under consideration by the Council. We have such men as Taylor, Lusk, and Folin and others who are most competent to advise along this line, and their advice should be sought and followed before we really feel the necessity of regulating food distribution and consumption.

7. *Preserved Foods.*—The Canning Association has placed in the hands of the Harvard Medical School the sum of $20,000 a year to be used by Rosenau in studying their products. Rosenau is working under a Committee selected by the National Research Council. This work will include everything pertaining to preserved foods, the possibility of their contamination and of food-poisoning resulting therefrom.

8. *Soldiers' Clothing.*—So far there has been no important criticism of the present clothing, nor suggestions concerning improvement. Color, weight, durability, imperviousness to moisture, are some of the factors that must be taken into consideration.

9. *Infected Wounds.*—Our veteran surgeon, Keen, is preparing a report upon knowledge acquired during the present war in the treatment of infected wounds. Surgeons who have been to the war zone in Europe are requested to communicate with Dr. Keen.

10. *Shock.*—Much good work has been done, and some of the best of it by American investigators on shock. We have such authorities as Porter, Crile, Cannon, Janeway, and others, and it is expected that such men will collect and arrange for service all of the best information along this line.

11. *First-Aid Dressings.*—Whether the first-aid package carried by the American soldier now can be improved upon is a question. There are rather complicating statements from abroad concerning the use of iodine in first aid. So far as it can be ascertained, it seems that iodine was at first used too abundantly and rather ignorantly, and that it did more harm than good. Further information along this line is desirable.

12. *Fatigue.*—It is highly desirable that some method can be found by which, on the examination of recruits, the man who is likely to suffer from heart-strain or from exhaustion should be recognized and should be assigned to the lighter duties. A man easily fatigued is not only unfit for the fighting line, but is a direct detriment to his companions on that line. Several prominent physiologists and clinicians are at work on this subject.

13. *Occupational Diseases.*—Edsall of the Harvard Medical School has been asked to associate with himself such other experts on this subject as he may need, and to investigate the matter. We are especially concerned with those diseases which afflict munition manufacturers.

14. *Venereal Diseases.*—This is one of the biggest problems with which the Council has been confronted in the medical line. At present every recruit is given the Wassermann test. A positive finding does not necessarily exclude the man, but it becomes a matter of record. So far as medical officers know, there are no cases of transmission of syphilis directly from soldier to soldier. Gonorrheal ophthalmia is spread in some instances by infected towels. Whether or not in case of assembling a large army some earnest attempt should be made to exclude dissolute women from the vicinity of camps is a question of importance. A large Committee has charge of this matter, and suggestions will be gladly received from any source. It will certainly be a great misfortune if we assemble in camps the flower of the nation and have these young men contaminated with venereal disease.

15. *Recruits.*—In assembling a large army rather suddenly, much will depend upon those who examine recruits. Such examinations should be both rapid and accurate, and the result will depend upon the training of the officer who does it. With proper training, men can be examined both rapidly and thoroughly. Without proper training, no amount of time will give good results. This is a matter of great importance. We understand that Canadian medical officers enlisted many thousands who, after reaching England, were found to be absolutely unfit, and had to be returned to Canada. The unfit man is not only no good as a soldier, but is a detriment and a hindrance in every way. He must be fed, clothed,

and cared for, and he becomes a burden for the present, and a pensioner in the future.

16. *Manufacture of Salvarsan, and Other Articles Now Under German Patent.*—This is a chemical rather than a medical question. Salvarsan is made by the Massachusetts State Board of Health and has been made by Shamburg, of Philadelphia. The question of infringement of patent is a legal one, and will have to be taken care of by the Legal Department of the Government. Attention has been called to the necessity of making cocaine substitutes and chemists in different parts of the country have been called upon to prepare for this work. The Government should import as soon as possible such quantities of opium and cinchona as may be needed.

17. *Medical Plants.*—This subject properly belongs to the Committee on Botany of which Professor Coulter of the University of Chicago is Chairman. There are certain plants of great medicinal value, such as belladonna and digitalis for which we depend largely upon importation. These plants have been grown more or less in this country by the Bureau of Plant Industry in Washington, by the Universities of Wisconsin, Minnesota, and Oregon, and by some commercial houses. The National Research Council would like information along this line.

18. *Vermin.*—Lice infected many of the soldiers on the Texas border. Of course, these lice did not carry the typhus virus, and consequently did not disseminate typhus fever. Much has been done along this line in Europe, and Strong, who conducted the crusade against typhus fever in Servia, will be depended upon for leadership in combating typhus fever and other diseases disseminated in the same way. A cresol preparation has been found to be most effective.

19. *Malaria.*—Some years ago Major Craig of the Army Medical Corps wrote a monograph on the Prophylaxis of Malaria as practiced by the army medical officer. The National Research Council will request that this monograph —possibly revised and brought up to date—be reprinted in sufficient numbers to be placed in the hands of every medical officer in the Reserve Corps. Certain sections of our country will require from medical officers a knowledge of the preventive measures for combating malaria.

20. *Flies.*—Experience on the Mexican border has shown that the fly problem has not been entirely and satisfactorily solved. One trouble lies in the fact that the area immediately around the military camp, and beyond military jurisdiction, is often in a bad sanitary condition. Flies breed in these localities, and spread to the camps. It has been suggested that in case large troops are assembled, the Public Health Service should be put in control of the sanitation of the surrounding country. The patrol of this service should be as extensive and as thorough as the necessities of the case demand. Possibly the Public Health Service might banish prostitutes as well as other pests from the surrounding country.

21. *First-Aid Dressing Stations.*—The object of the Council has been to learn what has been done along this line in Europe, and, if possible, suggest improvements. The first-aid rendered a wounded man influences greatly not only his

subsequent condition so far as pain is concerned, but often has a determining effect upon the final result.

22. *Motor Laboratories.*—Motor laboratories are employed in France. We intend to copy these, and to improve upon them if possible. It is desirable to learn as accurately as possible what these laboratories should carry.

23. *The Disinfection of Ambulances, Cars, and Other Vehicles Used in the Transportation of the Wounded.*—These vehicles become soiled with dirt, blood, and fecal matter. What are the best methods of cleaning and disinfecting them?

24. *Protection of the Ear From the Noises of Battle.*—Much work has been done upon injuries to the ear caused by explosions. There is considerable literature concerning this subject. An American physician, Wilson, has given special attention to this subject, and it is hoped that he will advise the Council in this and in any other matters with which his experience abroad may have acquainted him.

25. *Tuberculosis in War.*—How closely should the recruit be examined for the discovery of early tuberculosis? Experience in France seems to show that certain cases of tuberculosis have been benefited by army service, while others have been injured. Life in the trenches has developed latent tuberculosis, while army life in the open has improved many cases of this disease, and, indeed, apparently cured them. At present it seems wise that in the examination of recruits the closest attention should be given to incipient tuberculosis; that this should not necessarily exclude a man from service, but be of value in determining the line of service to which he is assigned. Then there is the big question in France now of what is to be done with the soldier who develops tuberculosis. Shall he be sent to a sanitarium, or an open air camp, or shall he be sent home? If he has open tuberculosis, shall he be kept under supervision and so guarded that he will not scatter the infection, or shall he be allowed all of the freedom of civil life? These are big and important questions.

26. *The Psychoses of the Soldier.*—To what extent should mental tests be employed in recruiting? Should men who evidently are of unstable organization be received into the service, and if so, into what line of service may they be admitted? The Council hopes for advice from our specialists in nervous diseases on this matter.

27. *Hastening the Healing of Wounds.*—What can be done along this line? The Council will look to Carrel and other experts for advice. Robertson of the University of California has extracted from the anterior lobe of the pituitary body a substance which he calls tethelin. This substance has a pronounced effect upon the growth of animals, and it has been suggested that it might be of value in hastening the healing of wounds.

These problems have been taken up by the National Research Council. The Council will gladly receive suggestions upon these and any other scientific problems which may appear to anyone. Suggestions, help, or information of any kind will be gladly received by the Medical Committee of the National Research Council. Address—Room 908 Munsey Building, Washington, D. C.

—*V. C. V.*

Are We to Forget the Lessons of 1898?

THIS is a question now being asked by medical men all over this country. We have no desire to recall the sad story of typhoid fever epidemic among our soldiers in 1898, unless we may profit by doing so. It may be well for us to remember that out of a total of 200,000 enlisted men in that war, more than 20,000 developed this disease. But, says one, vaccination now prevents altogether, or greatly lessens the chances of developing typhoid fever, and such an epidemic can never again occur. This may be true, and is undoubtedly partly true, at least of typhoid fever, but there are other diseases for which, unfortunately, we have no protective vaccination. Some of these diseases are diarrhea, dysentery, both bacillary and amebic, scarlet fever, measles, various forms of meningitis, poliomyelitis, pnuemonia, tuberculosis, etc. All infections have not yet been conquered. Among the causes of the fearful diseases of 1898—and the causes were many—was the lack of authority on the part of the medical officer. There is abundant evidence of this in various government documents. In the "Report on Typhoid Fever in United States Military Camps in 1898" the evidence that the superior authority of the line officer was responsible in many instances for the unsanitary condition of the camps is abundant. This report tells us that many commands were unwisely located, and often this was done in the face of remonstrances on the part of the medical officer. Medical officers of the Seventh Army Corps generally condemned the location at Miami, and yet regiments were kept on this site until they were much reduced by illness, and at Chickamauga some regiments were placed on ground so rocky that the construction of latrines of proper depth and width was impossible. Other camp sites received the surface washings from adjacent commands. Some were contracted into half the regulation space. Many regiments were compelled to remain on the same site until the soil became badly polluted, notwithstanding the fact that there were many broad acres around about, and no hostile army was nearer than Havana. From this report we make the following quotation: "There were regiments at Chickamauga that did not move a tenth of an inch from the time of arrival in May to that of departure late in August. Requests for change in location made by medical officers were not always granted. As an illustration under this head we may call attention to the official records of the Fifth Pennsylvania. This command reached Chickamauga Park May 20, and was, unfortunately, located on low ground. Requests for a change in location were repeatedly sent in during June and July. The soil became muddy; the camp received the washings from camps above; the sinks rapidly filled with water and overflowed, and still requests for change in location were not heeded until August 12. As we have seen, some of the regiments were improperly located from a sanitary standpoint. This was done by superior line officers, and sometimes in the face of protests from the medical officers."

This report advised that greater authority be given medical officers in all questions relating to the hygiene and sanitation of camps, and now, as we are going into another war, the line has one general officer for every 167 commissioned officers, while the medical corps has but one, whatever the number of commis-

sioned officers may be, and in an army of one million, the number of commissioned medical officers will be not less than seven thousand.

The medical profession requests that one-half of one per cent of commissioned officers in its corps have the rank of general officers. This seems a modest request, and is allowed in the navy; but, for some unknown reason, has so far been denied the army. One who has served in the medical corps can understand and thoroughly appreciate the hesitancy with which a lieutenant in that corps may recommend to a Colonel of the line that a camp site be changed, or that some other sanitary improvement is desirable; and one who served in the medical corps in 1898 knows full well the reception such a recommendation frequently met at that time, and he can guess at the reception it is likely to receive in the future under similar conditions. If any one has doubt concerning the attitude of many line officers of high rank in 1898 towards the recommendations of medical officers, he should read the testimony of Major General Brooke and other officers in command in the camps in 1898. This testimony may be found in the volumes of the Congressional Inquiry into the "Conduct of the War Department in the War with Spain," generally known as the Dodge report.

The Commanding Line Officer at Chickamauga took no pains in his testimony to show his contempt for the advice of his own medical officers, and this contempt and disregard constituted large factors in filling the hospitals and graves with typhoid cases. We have not place here to quote largely from this testimony, but a few sentences of the testimony of General Brooke may be given:

"Q.—Had any of the wells, General, been condemned by the Medical Department prior to your leaving (Chickamauga)?

"A.—By alleged Medical Departments. Two of them were erroneous, I believe, after investigation made by myself. The one in front of a South Carolina Regiment which, I believe really to have been perfectly pure water. There was afterwards discovered a surface well which had been walled up and water slipped in from which this Regiment—this was reported to me—used the water. That well was not far from a large sink, and possibly on lower ground. I never could understand from my knowledge of rocky strata how that well could have been contaminated. Another well lying on the road between Alexander House and Jays' Mill was also condemned. I drank of that well water every time I passed it until somebody broke the pump to pieces. I suppose it was some of our energetic medical fraternity who had spent their time in finding that there was a suspicion of these two wells—and then I did not bother further about it."*

On the following page there is a statement of the unsanitary condition of Camp Thomas made by the medical officer of the Twelfth New York Infantry. The commanding Line Officer was so incensed at this report that he said: "If you will give me a copy of that report, I will see that that young man goes before a court-martial for the sort of statement he has made there if he is not protected by this commission."

On July 17, 1898, the Chief Medical Officer at Chickamauga addressed a letter to the Adjutant General containing recommendations concerning the improvements of sanitary conditions. In brief the letter contained the following recommendations:

*Conduct of War Department in War with Spain, vi, 3080.

1. That the signal corps which had occupied the same site for several months, and which was crowded, should be moved.

2. That selected places should be designated as dumping grounds, and all the waste should be collected and deposited on these places instead of being scattered through the camp.

3. That so far as possible all camp sites should be changed.

4. That the hospital of the First Division of the First Corps be moved from the unsanitary position they occupied to a more healthful location.

5. That the village of Lytle, which was a sanitary menace to the troops, should be cleansed.

6. That all condemned sources of water supply should be effectually closed.

7. That only filtered or boiled water should be used by the soldiers.

8. That all hucksters selling doubtful food or drink should be expelled from the camp.

9. That there should be careful supervision of all food and drink sold in the canteens.

These recommendations made in July were unheeded at the time.

In his testimony, General Brooke spoke of the letter containing the above recommendations as follows: "I did not regard his letter in a very serious sense. I do not know how he came to write it. There was much complaint in that camp from men of his own profession as to his action. He caused me more trouble and annoyance than anyone ever did."

Had the recommendations contained in this letter which annoyed the Senior Line Officer been taken seriously in July, the fearful harvest of sickness and death in August might have been averted.

Nineteen years have passed since our little war with Spain, and we have crossed the threshold of a great war with Germany, Austria, Bulgaria and Turkey. This war begins with the medical officer possessed of no more authority than he had in 1898. Will his recommendations be as futile as they were then? The medical profession has always been responsive to its country's demands, whether in war, in pestilence, in flood, or in famine. Conscription has never been necessary to fill its quota. Medical officers will do their best and will present their recommendations to superior line officers, but they realize that these recommendations are likely to receive scant attention, and that the medical officer will be compelled to work under a heavy handicap. The government stamp placed upon the medical officer indicates the opinion that the government has of the value of his services, and that his recommendations will receive from line officers any different consideration from that accorded them in 1898 is not probable. At present the Army Medical Corps has no representation on the General Staff or in the War College.

Will it be possible that camp sites, both small and great, will be selected as they were in 1898 without consultation with the medical corps? And are we justified in feeling that we may have some reminders of the experiences of 1898? According to the testimony of the Surgeon General recently, given before a medical committee, the relative number of trained medical officers is not as great now as it was at the beginning of the Spanish War. We had then seven per thousand. We have now about five per thousand. —*V. C. V.*

Ambard's Coefficient

THE methods which have been developed in recent years for the analysis of blood in normal or pathological conditions have opened many fields of investigation. Perhaps the most important of these, from the standpoint of medicine, is the problem of renal function. Not long ago, the clinician had to be content with a very elementary analysis of the urine in cases where the kidneys were suspected of being diseased. The methods for the analysis of the blood for the urinary constituents were not suitable for use in the clinic, and the simple procedure of drawing blood from a vein was thought to be a rather serious measure, because of fear of introducing bacteria into the circulation. Thanks to the development of first-class chemical methods for the quantitative determination of the urinary nitrogenous bodies in small quantities of blood, and the general use of venous puncture brought about chiefly through the development of the Wassermann reaction, our knowledge of the intermediary metabolism of the proteins in disease has been greatly extended. As it is now possible to determine with ease the quantity of the urinary constituents in both blood and urine, it is not surprising that numerous researches have been directed to show the relationship which exists between them.

Our knowledge of the kidney is still in an incomplete state. There are two schools of thought in regard to the fundamental process which is responsible for the excretion of urine, i. e., the physical and the vital schools. Perhaps the majority of physiologists believe that both physical and vital processes play a role. Certainly there are many phenomena in the excretion of the urine which cannot be adequately explained at present either on a purely mechanical or on a vital basis. Nevertheless, if physical processes play the most important role in the secretion of the urine, it should be possible to formulate fairly definite laws which will mathematically express the relationship of the concentration of the urinary bodies in the blood and the urine, and the rate of their excretion by the kidney. In the urine we find a concentrated solution of nitrogenous waste material; in the blood the reverse is true. For years it has been thought that there is no definite relationship between the concentration of urea in the blood and the rate at which the kidney secretes the urea. Undoubtedly the blood flow and the blood pressure in the kidney are important factors in this connection, but they cannot be experimentally determined.

About six years ago two Frenchmen, Ambard and Weill,[1] announced some laws which reduce the study of renal function to physical laws. They believe that the urea in the blood acts as a stimulus to the renal cells, and that the rate at which the urea is secreted varies with the strength of this stimulus. In support of this postulate they collected a number of cases in which the concentration of the urea in the urine was alike, and they found that the rate of the excretion of urea in these cases varied directly as the square of the concentration of urea in the blood. This may be mathematically expressed in the form of the simple proportion:

$$\frac{(\text{Grams of urea per 100 c.c. of blood in case A})^2}{\text{Grams of urea excreted in the urine per hour in case A}} = \frac{(\text{Grams of urea per 100 c.c. of blood in case B})^2}{\text{Grams of urea excreted in the urine per hour in case B}}$$

According to Ambard and Weill, the rate of the circulation of the blood through the kidney is the factor which governs the concentration of the urine. A dilute urine is a sign of a fast circulation, a concentrated one of a slow circulation. In connection with this, they found a number of cases in which the concentration of the urea in the blood was alike, and in these cases the rate at which the urea was excreted by the kidney varied inversely as the square root of the concentration of the urea in the urine. This may be mathematically expressed in the form of a proportion:

$$\frac{\text{Rate of excretion of urea in the urine in case A}}{\text{Rate of excretion of urea in the urine in B}} = \frac{\sqrt{\text{The concentration of the urea in the urine of case B}}}{\sqrt{\text{The concentration of the urea in the urine of case A}}}$$

In other words, the greater the concentration of the urea in the urine, the blood urea remaining constant, the slower the rate of elimination of the urea. By combining the two laws they obtain an equation which gives a constant, this constant expressing the relationship between the rate of excretion of the urea in the blood and in the urine. In order to make this constant standard in all cases, they adopted a standard body weight of 70 kilos and a standard concentration of the urine of 25 grams per liter. These corrections they include in the formula, which reads as follows:

$$K = \frac{Ur}{D \times \frac{70}{P} \times \frac{\sqrt{C}}{\sqrt{25}}}, \text{ in which:}$$

K = coefficient of urea excretion (Constant of Ambard).
Ur = grams of urea per liter of blood.
D = output of urea in grams per 24 hours.
P = weight of the patient.
C = grams of urea per liter of urine.
70 = standard weight.
25 = standard concentration of the urine.

The average value for this constant in normal individuals they found to lie between .06 and .09. In cases of renal disease the coefficient is usually raised. Maclean and Sellings were the first in this country to use the coefficient of Ambard as a test of renal function. By using methods for analysis superior to those used by Ambard, they found that the coefficient of Ambard is a little low. They also propose a modification of the formula of Ambard which in no way changes the principles involved, but expresses the normal value in terms of 100. Their formula is

$$\frac{\text{Grams urea per 24 hours excreted in urine}}{\text{Weight of body in Kg.}} \times \frac{\sqrt{\text{grams urea per liter excreted in urine}}}{(\text{Grams urea per liter of blood})^2} \times 8.96 = \text{Index of excretion.}$$

In the above formula the standard weight and standard concentration of the urea employed by Ambard are present in the factor of 8.96.

Using this formula Maclean[2] computed the relation of the rate of urea excretion to the concentration in the blood in 107 observations on individuals with normal excretion. From these data he concludes that the rate of the excretion of urea can be measured directly in terms of the normal by the use of the modified

Ambard's coefficient. The normal average concentration of urea in the blood in the above cases varied between about .2 and .5 grams per liter in the same or different individuals, and the rate of excretion appeared to be controlled by this concentration and by the rate of water excretion. Below values of .3 grams per liter the laws do not hold so closely, since there is a tendency in such cases towards a higher rate of excretion. He calls particular attention to the larger number of cases (71) in which the blood urea is between .3 and .5 grams per liter since it is within these limits the blood urea figures may be normal or signify retention. Of these, 52 gave an index within ten per cent of the range of normal values, which may be considered, he believes, to lie between 80 and 125; 69 of these, i. e., 97 per cent, come within a range of 25 per cent of the normal value. Of the 107 cases reported only three had an index below 80, which he believes indicates impairment of renal function.

As a means of testing the validity of Ambard's laws, Maclean calculated in each case, in addition to the index of urea excretion, the following formula:

$$\frac{\sqrt{\text{Urea excreted in 24 hours}} \times \sqrt{\text{Concentration of urea in the urine}}}{\text{Weight}}$$

This formula expresses Ambard's laws in the simplest form, and it is not distorted by the addition of constants used in the coefficient. There is quite a variation in the index he obtained by this formula, and this is true even where one would expect the laws particularly to hold, as in cases where the concentration of urea in the blood was the same. The most marked variation is found in the cases where the blood urea is below .3 grams per kilo, in which there are variations of 33 per cent of the value of the normal figure, which Maclean fixes at 30 as this corresponds to 100 in the complete formula. In this form it is apparent that, by the use of the square of the urea in the blood as a part of the denominator, a somewhat wide variation in the value of the constant or percentage of normal excretion will be obtained, just as is the case with the constant when we use the square of the urea of the plasma in expressing Ambard's first law. The normal limits of variation once established, the modified index of Maclean is better, since it expresses the urinary urea excretion in terms of the per cent of normal. With the higher concentrations of urea the coefficient is sufficiently constant, Maclean believes, to be of use in testing renal function by the use of the complete formula proposed.

Recently Addis and Watanabe have published a good series of observations on normal individuals, in which the two separate laws on which Ambard bases his coefficient are more thoroughly tested than by either Ambard or Maclean.[3] They have arranged their cases in two classes: one in which the cases are classified in groups having the same concentration of urinary urea, and another in which the groups are made of those having the same concentration of blood urea. They hold that if Ambard's postulates are true, each instance within the different groups must possess the same constant when the laws are applied. They conclude from their results that, since the variations found are entirely too great to be due to experimental error, factors other than the concentration of the blood urea must commonly intervene in the process of urea excretion.

Addis and Watanabe rightly call attention to our lack of complete knowledge

of the factors governing the excretion of urea by the kidneys. They feel that the impression that these factors are known and measurable with mathematical accuracy would be likely to retard further investigation. The constancy of the combined formula, which after all appears to be only roughly approximate, is due in large part to the mathematical construction, and also to the fact that any increase in the concentration of urea in the blood is usually accompanied by an increased rate of urea excretion. The factors which are most variable occur as the square or the fourth roots of their values, and thus the disturbing effect they produce on the constancy of the resultant of the formula is greatly reduced, while the most constant factor, the concentration of urea in the blood, is used without modification. As these critics suggest, in such a complex mechanism it is very probable that other factors are of great importance in controlling the rate of urinary excretion. Many of these factors cannot admit of mathematical expression.

It may be that Ambard's laws roughly express in mathematical form one of the important factors in urinary excretion. In the healthy normal kidney, however, there are vital factors which even Ludwig, who first formulated the mechanical theory of urinary excretion, was forced to accept. It may be that the wide variations which all careful workers find present in the coefficient in normal individuals is simply an indication that the physico-chemical factors are not relatively so important in the normal kidneys as they are when the vitality of the kidney is decreased.

In pathological conditions in which the kidney's excretory power is diminished, we should naturally expect an increase in the concentration of the urea in the blood, or a decrease in the concentration of the urea in the urine and an increase in blood pressure, if physical laws are to compensate for the loss of the vital activity. Most of these factors are present in chronic nephritis. In this connection the work of Mosenthal[4] is most illuminating. He finds that the diseased kidney can no longer concentrate the urine. Is it not significant that the ability of the kidney to concentrate the urine was the point which Ludwig could not explain upon a mechanical basis?

The French have used the coefficient for some time as a measure of renal activity. Maclean has reported a series of observations on patients suffering with renal disease. Very recently Lewis[5] has published an extensive report in which he discusses the clinical value of the coefficient. He finds, as the previous observers have done, that the normal variations are rather wide and are subject to many disturbing influences. In hospital practice he has observed, however, that the variations in the normal figure are small, and that in cases where the metabolism is much increased, as in fevers, in exophthalmic goiter, in hypertension with early changes in the renal arterioles, and in early chronic diffuse nephritis, there is a depression of the coefficient of Ambard. This depression he believes indicates an increase in renal activity. He finds that the coefficient is raised in cases where there is evidence of decreased metabolic activity, as in myxedema. Similarly he finds that, in myocardial insufficiency and in nephritis with renal insufficiency, the coefficient is raised. This appears to indicate that, when the vital activity of the kidney is in any way disturbed, the physico-chemical factors at once play a relatively greater part in the renal excretion. He finds a

marked uniformity in the coefficient and the results obtained by the phenolsulphonephthalein test in all stages of nephritis, and believes that the test has considerable prognostic value.

Lewis takes issue with Addis and Watanabe on the point that the concentration of the blood urea is really the factor which determines the constancy of the coefficient, for he cites cases in which the blood urea was markedly reduced by dietary measures without any effect on the value of the coefficient.

This problem is very interesting, but there are many points which must be subjected to most severe scrutiny before the coefficient is accepted as really being anything more than a rough indication of what the vital activity of the renal cells is, or as being superior in any way to the phenolsulphonephthalein test, or to the more physiological test advocated by Mosenthal. With the use of the newly developed methods of blood and urine analysis for urea, we hope that future work will be able to differentiate clearly between the vital factors of renal activity and the factors which the laws of Ambard attempt to express.

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[3]Addis and Watanabe: Jour. Biol. Chem., 1916, xxiv, 203.
[4]Mosenthal: Arch. Int. Med., 1915, xvi, 733.
[5]Lewis: Arch. Int. Med., 1916, xix, 1.

—*R. G. P.*

Pulmonary Osteoarthropathy

HYPERTROPHIC pulmonary osteoarthropathy is an interesting condition not because of its effect upon the life of a patient but because of its associated organic diseases. Described first by Marie (1890), and shortly afterward by Bamberger, it has become one of the many interesting anomalous bone diseases the causes of which are not known. It is of clinical interest because of the resemblance it gives, in the hands particularly, to acromegaly; and because of the hint it gives of thoracic, and especially pulmonary, trouble. It has been described as frequently associated with chronic pulmonary tuberculosis, with bronchiectasis, with pleural empyema, and with mediastinal tumors. Nevertheless, a recent textbook on tuberculosis states that in 2,300 tuberculous patients not a single case of osteoarthropathy was observed.

Recently, that is to say within the past ten years or so, several interesting reports have come from Locke[1] and Brooks.[2] These are summarized, in the latest account of the disease, by Kessel.[3]

Kessel has made radiographic studies of the hands, feet, all of the long bones, the bones of the pelvis, and in some instances the shoulder girdle and cranial bones, with the interesting result that he has found evidences of hyperplastic growths connected with the bones in 32 cases, and has found evidence, in addition to that given by Janeway[4] and Locke, that simple clubbing of the

[1]Locke: Arch. Int. Med., 1915, xv, 659.
[2]Brooks: New York Med. Jour., Sept. 27, and Oct. 4, 1913.
[3]Kessel: Arch. Int. Med., 1917, xix, 239.
[4]Janeway: Am. Jour. Med. Sc., October, 1903.

fingers and hypertrophic osteoarthropathy are stages of the same process, and not different processes as certain French and German authors believe.

The etiologic factors are only guessed. It is usually conceded, says Kessel, that prolonged venous congestion is the cause of the ordinary clubbed fingers, and Brooks, following Ziegler, believes that a continued peripheral hyperemia is produced by compression of the lung capillaries in pulmonary, pleural, and mediastinal disease, and this in the course of time leads to hyperplasia of the periosteum and connective tissue. In addition to this hyperemia a circulating toxin probably plays a role, say the writers. This it may be said is all guess work.

However the changes are produced, they consist in a progressive ossifying periostitis, usually manifesting itself in the distal ends of the diaphyses of the long bones and later involving the other bones of the skeleton. The earlier stages, or the milder forms of the disorder, appear to be mere hypertrophy of the soft tissues with thickening of the nails. Many patients also show a globular nose and evidence of thickening of the subcutaneous tissue in the malar regions.

Kessel's cases arrange themselves in three groups. In the first are five patients with simple clubbing of the fingers without bone changes. In the second are seventeen patients with clubbing of the fingers and bone changes. In the third are ten patients with clubbed fingers and changes in the long bones. The bone changes do not run parallel, in severity, with the tuberculous process.

—P. G. W.

The Rank and Authority of the Medical Officer

WHEN Stanton was Secretary of War, and Hammond, Surgeon General, early in the Civil War, the latter made a request of the former for advanced rank for medical officers. The great Secretary of War replied with a question: "Will increased rank make your medical men better doctors?" The Surgeon General replied with another question: "Does increased rank make Line Officers, Quartermasters, and those in other corps more proficient?"

There are two important considerations in regard to the rank and authority of army medical officers. In the first place, the higher the rank obtainable, the better the class of young physicians attracted to the corps. When a young man knows that whatever he may do, however skillful and energetic he may be, whatever discoveries he may make, whatever sacrifices he may undergo, the rank of Colonel, with a pay of about $5,000 is the best that he can possibly look forward to in his old age, it must be acknowledged that the temptation to enter the army medical service is not great.

In the second place, and this is of more importance, rank in the Army necessarily means much. A request or a recommendation from a Colonel or a General will receive more consideration than when it comes from a Lieutenant. Much of the disgrace of 1898 and the disregard shown their recommendations by superior line officers, was due to the lack of rank and authority among medical men.

—V. C. V.

The English Recognize the Importance of Giving Authority to Medical Officers

IN 1904 the English War Office was reorganized by a committee, the chairman of which was Lord Esher. In this reorganization, no provision was made for a representative of the Medical Army Corps on the General Staff, or what corresponds to our War College. At the time the Surgeon General complained of this action. In reply to this complaint Lord Esher's committee stated that while too much importance could not be attached to the sanitary service of the army in peace or in war, the committee could not accept the views of the Surgeon General. Lord Esher's committee continued, "The Army Council is not, and can not be, a representative body as regards the several arms and departments. The Royal Army Medical Corps exists to serve the Army in a most important capacity, but the first object must be to create and maintain an Army, and this is the function of the Army Council. To admit the principle of representation would destroy the character of the Council."

This was the opinion of Lord Esher in 1904. Recently (*London Times*, February 3, 1917) Lord Esher writes as follows: "How much of the suffering undergone by our soldiers since the war began has been due to the shortsightedness of my committee, and notably of myself, will never be known. Certainly the control of the Adjutant General's branch over the Royal Army Medical Corps, was and is responsible not only for the early failure to grip the medical factors of the war, but they hampered conditions under which the Surgeon General has worked. His triumphs, and those of the Royal Army Medical Corps have been achieved in spite of obstacles that the subordination of science to ignorance, and of elasticity to military discipline explains, but can not justify."

—*V. C. V.*

Intestinal Obstruction

THE cause of the rapidly developing and quickly fatal toxemia which follows acute intestinal obstruction has never been satisfactorily explained. Numerous theories have been formulated, many of which are based upon experimental data, but they differ widely. Clinical and experimental evidence fails to show the presence of a bacteriemia in many cases. In the normal bowel, substances are found which are toxic when injected into the blood stream, and experimental evidence indicates that the substances obtained from the obstructed gut are more toxic than those from a normal one, but the relationship of these toxic substances in the intestines to the symptoms and the factors involved in the production and the absorption of the toxic materials are unsettled. Recently several papers have appeared which throw some light upon the question.

Whipple, Cook, and Stearns report experiments in which they have injected a protein substance (proteose) obtained from the contents of isolated closed loops of intestines in dogs and from those of the intestines of clinical cases of intestinal obstruction. They find that there is a definite increase in the nonprotein nitrogen of the blood following the injection of the proteose substance.

Likewise they find an abnormally high nonprotein content in the blood of cases suffering with intestinal obstruction and in dogs with closed intestinal loops. The proteose intoxication is accompanied by the usual symptoms of obstruction; viz., vomiting, diarrhea, low blood pressure and a temperature reaction. They believe that the proteose produces a tissue reaction, which disturbs the delicate equilibrium of the numerous physicochemical reactions in the tissue cells, and that the results of their experiments indicate that the symptoms of intestinal obstruction are produced by the absorbed proteose in the obstructed bowel. They have been able to show that repeated injections of sublethal doses of the proteose material confer upon an animal a relative immunity to its toxic action. Dogs in which such an immunity has been established survive a closed loop of intestine in the abdominal cavity, or an intestinal obstruction, longer than animals which are not immune. The immune animal can also withstand the action of a lethal dose of proteose substance. An examination of the urine in these cases shows that during the intoxication and for some time following the reaction, there is an increased excretion of nitrogen above the fasting level, and that this increase is, in general, proportional to the severity of the reaction. They believe that the increase in nitrogen excretion indicates a general breaking down of tissue proteins and that this plays an important role in the intoxication.

In the same number of the journal in which the above mentioned experiments appear, Dragstedt, Moorhead and Burcky, working in Carlson's laboratory, report some very interesting and important experiments which contribute to the support of the proteose theory of intoxication in obstruction. A large number of observations were made on dogs in which loops of intestines were isolated and the integrity of the bowel restored by joining the free ends. In all the cases in which the loop was closed, the animal died with the symptoms of acute intoxication or peritonitis. Loops made high up in the bowel were more rapidly fatal than those made lower down. In one series of cases the loops were thoroughly washed out with water and ether before they were closed. A fair percentage of the animals recovered and lived normally. Examination of the loops showed that bacteria were present in the contents. Sudden obstruction of the blood supply of these loops resulted in acute symptoms of intoxication and obstruction, and then death. In a number of dogs, loops of intestines were isolated and after being thoroughly washed were replaced in the abdominal cavity without being closed. Some of these animals lived. Later examination showed that the ends of the loops had closed and that the contents were sterile. Occlusion of the blood supply to these loops caused no symptoms. In another series, loops from the duodenum and the jejunum, having open ends and without being washed, were dropped back into the abdominal cavity. Three dogs, or one-half the number in the series, recovered. Thirty days later, examination showed the loops closed and distended with fluid.

The experiments are very instructive, since they demonstrate that the mere presence of bacteria alone in the loop, is not sufficient to cause symptoms, and that the secretion of the bowel is not the toxic agent. They indicate that besides bacteria, there must be present in the bowel toxic products resulting from the action of putrefactive bacteria on necrotic tissue to give symptoms of obstruc-

tion. Any interference with the blood supply when bacteria are present produces tissue necrosis. This condition simulates acute obstruction in man, in which there is an accompanying occlusion of the blood supply to the part (volvulus, strangulated hernia, etc.). The experiments seem to show that the toxemia which is produced by a closed intestinal loop without interference with the blood supply, is not similar to that found in intestinal stasis.

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—*R. G. P.*